Original Article

Usage Pattern and Serum Level Measurement of Amikacin in the Internal Medicine Ward of the Largest Referral Hospital in the South of Iran: A Pharmacoepidemiological Study

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Abstract

Background: The inappropriate use of aminoglycosides has harmful effects such as the development of resistant pathogens and the incidence of nephrotoxicity and ototoxicity. Therefore, drug utilization evaluation of these drugs may improve their usage remarkably. The aim of this study was to assess the usage pattern of amikacin in an internal medicine ward.

Methods: This cross-sectional study was conducted in the Internal Medicine Ward of Nemazee Teaching Hospital, Shiraz, Iran, in 2011. The guideline for amikacin use was approved by the institutional Pharmacy and Therapeutics Committee, and the study criteria were developed to assess several parameters involved in amikacin therapy such as appropriateness of drug use, dosage, duration of therapy, toxicity monitoring, and serum concentration assay. Serum concentration was assayed using a Cobas Mira AutoAnalyzer. Clinical and paraclinical parameters such as glomerular filtration rate, culture, microbial sensitivity, white blood cell count, and fever were collected.

Results: Sixty-three patients were evaluated. Fifty-seven percent of the patients needed dose readjustment; however, it was not performed for 89% of them. Culture between 48 and 72 hours after amikacin administration was not controlled for 79% of the patients. In 19% of the patients, optimum therapeutic effect was not achieved. The mean±SD of the trough and peak concentrations was 7.63±5.4 μg/mL and 15.67±7.79 μg/mL, respectively. Forty-five percent of the trough and 38% of the peak levels were within the therapeutic range. The overall adherence of amikacin usage to the guideline was only 48%.

Conclusion: To achieve appropriate treatment and prevent toxic effects, we recommend that pharmacokinetic dosing methods, amikacin guideline, and serum monitoring be considered.

What's Known

- Rational use of critical antibiotics such as amikacin is necessary.
- There is an individual variation in clinical response to amikacin, which has a narrow therapeutic index. Therefore, therapeutic drug monitoring of amikacin in any population and patient is strongly recommended.

What's New

- Designing a standard guideline for the first time for rational use of amikacin.

Introduction

Drug utilization is defined by the World Health Organization (WHO) as the "marketing, distribution, prescription, and use

of drugs in society, with special emphasis on the resulting medical, social, and economic consequences".[1] The goal of drug utilization evaluation (DUE) is to realize how and why drugs are used so as to improve appropriate drug use and health outcome.[2] The inappropriate use of antibiotics is one of the most important factors in the development of resistant microorganisms.[3]

Aminoglycosides are active against many aerobic Gram-negative bacteria, some aerobic Gram-positive bacteria, and certain mycobacteria.[4] The inappropriate use of aminoglycosides may result in the development of resistant pathogens and also nephrotoxicity and ototoxicity;[5] the DUE of these antibiotics can, therefore, improve their usage.

There have been several studies on the DUE of aminoglycosides, especially the therapeutic drug monitoring (TDM) of these drugs.[5-9] Ramesh et al.[5] evaluated the usage pattern of gentamicin, amikacin, and streptomycin with regard to their indication, dose, duration, safety, and cost in the pediatric ward of a teaching hospital in India and reported that the indication, dose, duration, safety, and cost of amikacin was appropriate in 73%, 87%, 86%, 50%, and 5% of the cases, respectively. Shrimpton et al.[6] performed an audit of amikacin and gentamicin prescription in a teaching hospital in U.K. by mainly focusing on the serum concentration assay of these antibiotics and reported that 63% of the courses of aminoglycosides had serum assays and that all the amikacin concentrations were within the recommended therapeutic range.

To the best of our knowledge, there is no comprehensive and specific study on the DUE of amikacin based on a definite standard guideline.

Amikacin is the most common aminoglycoside used in Nemazee Teaching Hospital, in the Iranian city of Shiraz. The pattern of microbial sensitivity to amikacin based on the report of Professor Alborzi Clinical Microbiology Research Center in Nemazee Teaching Hospital, Shiraz, is as follows: *Escherichia coli* (91%), *Pseudomonads* (80%), *Enterobacter* (69%), *Serratia* (65%), *Klebsiella* (64%), and *Acetobacter* (36%). Although the implementation of a standard guideline is one of the main strategies for promoting the rational use of antibiotics and also preventing the development of bacterial resistance,[10] no standard protocol exists for the prescription and administration of amikacin in our hospital. Thus, a standard guideline for amikacin usage was designed and the pattern of amikacin use was evaluated to determine the probable problems of its prescription and administration in Nemazee Teaching Hospital, Shiraz, Iran.

Patients and Methods

Setting and Patients

This cross-sectional study was approved by the Ethics Committee of Shiraz University of Medical Sciences (SUMS) and was conducted from April 2011 to December 2011 in Nemazee Teaching Hospital, Shiraz, Iran. This hospital is the most important referral teaching hospital affiliated to SUMS. All in-patients (age≥18 y) who had received intravenous (IV) amikacin at least for 3 continuous days were included in this study. Patients for whom amikacin was administered on fewer than 3 continuous days were excluded from the study. All the patients were monitored until they were discharged from the hospital.

Data Collection

The demographic data of the patients were collected using a data-gathering sheet which included the patients' age, sex, height, body mass index, ideal body weight, body surface area, date of admission, date of discharge, past medical history, drug history, and diagnosis. Also collected were the laboratory data of the patients comprising blood urea nitrogen (BUN), serum creatinine (S_{cr}), white blood cell count (WBC), heart rate, blood pressure, body temperature, urine analysis, cultures, and signs and symptoms of infectious diseases. Any adverse drug events due to amikacin that occurred during hospitalization were recorded.

The DUE data of amikacin were recorded in a log sheet designed by a clinical pharmacist based on the standard guideline[11-18] for amikacin usage in adults (table 1). This guideline was approved by the Pharmacy and Therapeutics Committee of Nemazee Teaching Hospital.

The clearance of S_{cr} was calculated according to the Cockcroft and Gault formula:[19]

Cl_{cr} (mL/min) = [(140- age in y) × (weight in kg)]/72 × (S_{cr} in mg/dL) × (0.85 if female)

Amikacin-induced nephrotoxicity was defined as a rise in S_{cr} more than 0.5 mg/dL over the baseline value in patients with normal S_{cr} baseline and more than 25% to 30% over the baseline value in patients with S_{cr} more than 2mg/dL.[15] Patients that had clearance of S_{cr} less than 60 mL/min were considered as renal failure.[12]

Nosocomial or hospital-acquired infections were defined as infections acquired during a patient's stay at hospital (those occurring 48 hours after the patient's admission), whereas community-acquired infections were defined as infections presenting at the time of hospital admission.[20]

Table 1: Amikacin usage guideline in adults

Indications

Aminoglycosides are antibiotics that are generally active against many aerobic Gram-negative bacteria and some aerobic Gram-positive bacteria and are principally used for serious infections, including bone and joint infections, intra-abdominal infections, respiratory tract infections, septicemia, skin and soft tissue infections, urinary tract infections, meningitis, mycobacterial infections, febrile neutropenic patients, and staphylococcal endocarditis

Dosing methods

Pharmacokinetic dosing

Sawchuk-Zaske method, Bayesian method, and Hull-Sarubbi nomogram

Conventional dosing

Usual dosage range (in normal renal function): IM, IV: 5-7.5 mg/kg/dose every 8 h

Indication-specific dosing

Endophthalmitis, bacterial (unlabeled use): intravitreal: 0.4 mg/0.1 mL NS in combination with vancomycin

Hospital-acquired pneumonia: IV: 20 mg/kg/d with antipseudomonal β-lactam or carbapenem

Meningitis (susceptible Gram-negative organisms): IV: 5 mg/kg every 8 h (administered with another bactericidal drug) or intrathecal/intraventricular (unlabeled route): usual dose 30 mg/d

Mycobacterium fortuitum, M. chelonae, or *M. abscessus*: IV: 10-15 mg/kg/d for at least 2 wk withhigh-dose cefoxitin

In renal impairment

Cl_{cr}≥60 mL/min: Administer every 8 h

Cl_{cr}=40-59 mL/min: Administer every 12 h

Cl_{cr}=20-39 mL/min: Administer every 24 h

Cl_{cr}<20 mL/min: Administer the loading dose, and then monitor the levels

Hemodialysis: 50% of the normal renal function dose after dialysis

CAPD: 15-20 mg lost per L of dialysate per d

CRRT: 7.5 mg/kg every 24 h

Route of administration

IV: Infuse over 30-60 min

Compatibility

Stable in different concentrations of dextran, NS, DW, LR, and mannitol

Monitoring

Before amikacin administration

Baseline S_{cr} and BUN

Baseline culture from the suspicious site of infection

Baseline urine input and output

Baseline WBC count and fever curve

After amikacin administration

S_{cr} every 2-3 d

Culture (48-72 h after administration)

Input and output of the patient's urine

Favorable response to antibiotics treatment according to:
Fever curve, WBC count, microbial culture, and clinical signs and symptoms regarding the site of infection

Hearing parameters

If audiometry is possible:
Baseline evaluation should be done up to 72 h following administration
Monitoring evaluation should be conducted 1 to 2 times per wk during treatment and also 6 mon after the cessation of treatment

If audiometry is impossible:
Follow up auditory (decreased hearing acuity in the conversational range or feeling fullness in the ears and tinnitus) or vestibular (loss of equilibrium, headache, nausea, vomiting, pressure vertigo, nystagmus, and ataxia) clinical signs and symptoms as the same time intervals as those of S_{cr} measurement

Discontinue amikacin administration or dose reduction in

Nephrotoxic patients

Nephrotoxicity is defined as:
Rise in S_{cr}>0.5 mg/dL over the baseline value in patients with normal S_{cr} baseline
Rise in S_{cr}>25 to 30% over the baseline value in patients with S_{cr}>2 mg/dL

Ototoxic patients

Ototoxicity is defined as:
Increase in pure-tone threshold from a baseline audiogram of at least 15 dB at 2 or more frequencies, or ≥20 dB at 1 or more frequencies

Table 1: (*Continued*)

Dose adjustment in conditions that affect amikacin pharmacokinetics
Renal failure, burns, obesity (>30% over IBW), cystic fibrosis, ascites/liver disease, premature infants, hemodialysis, peritoneal dialysis, elderly patients, and fever
Target therapeutic serum level is determined considering the type/site of infection, but in, general, the desired serum concentrations are as follows according to Quantex Amikacin Kit manufactured by Biokit)
Peak concentration: 15-30 µg/mL
Trough concentration: 1-8 µg/mL

IM: Intramuscular; IV: Intravenous; Cl$_{cr}$: Clearance of creatinine; NS: Normal saline; DW: Dextrose water; LR: Lactated ringer; S$_{cr}$: Serum creatinine; CAPD: Continuous ambulatory peritoneal dialysis; CRRT: Continuous renal replacement therapy; BUN: Blood urea nitrogen; WBC: White blood cell; dB: Decibel; IBW: Ideal body weight

Patients were considered as cured if they achieved both temperature and leukocyte count resolution with obliteration of the symptoms of infection during treatment.

Two blood samples were drawn from each patient: one sample 30 minutes after the completion of infusion (for peak concentration) and another 30 minutes before the next dose (for trough concentration). Serum peak and trough levels were measured using a turbidimeter AutoAnalyzer (Cobas Mira, Roche, Switzerland).

Statistical Analysis

A DUE log sheet of amikacin consisted of 12 variables. A score of 0 or 1 was given to each variable depending on whether the variable was evaluated as appropriate or inappropriate, respectively. This log sheet was completed for each patient. The total score was given to each patient by adding up the scores for each of the variables. The continuous variables were presented as mean ± standard deviation (SD), and the categorical data were shown as percentage. The data were analyzed using Statistical Package for the Social Sciences (SPSS), version 16.

Results

Sixty three patients were enrolled in this study. The mean±SD age of the patients was 55±22.2 years (range, 18 to 92 y). The demographic characteristics, clinical data, and amikacin prescription information are shown in table 2. Amikacin was mostly prescribed for the treatment of pyelonephritis (25%; n, 16) and pneumonia (25%; n,16).

Cultures from the site of infection were not controlled in any of the patients before amikacin prescription. Amikacin therapy continued for 87% (n, 55) of the patients based on the clinical judgment of the physician. Only in 13% (n, 8) of the patients 48 to 72 hours after amikacin administration were the cultures from the site of infection controlled, and amikacin therapy was continued based on microbiological sensitivity tests.

Table 2: Demographic characteristics, clinical data, and amikacin prescription information (n=63)

Variable	n (%) or Mean±SD
Age of the patients (y)	55±22.2
≤60	31 (49)
>60	32 (51)
Sex	
Male	30 (48)
Female	33 (52)
Duration of treatment (d)	8.80±6.00
Ideal body weight (kg)	47.13±3.40
Peak serum concentration (µg/mL)	15.67±7.79
Trough serum concentration (µg/mL)	7.63±5.40
Clearance of creatinine (mL/min)	
<20	11 (17)
20-59	37 (59)
≥60	15 (24)
Origin of infection	
Community acquired	58 (92)
Hospital acquired	5 (8)
Diagnosis/infectious disease	
Pyelonephritis	16 (25)
Pneumonia	16 (25)
Neutropenic fever	9 (14)
Urosepsis	6 (11)
Sepsis	4 (6)
Urinary tract infection	3 (5)
Cholangitis	2 (3)
[a]Others	6 (11)
Amikacin prescription based on	
Clinical judgment	55 (87)
Microbiological sensitivity tests	8 (13)

[a]Others: Catheter-associated infection, endocarditis, liver cirrhosis, lymphoma, meningitis, and skin infections

The DUE data on amikacin are summarized in table 3. Amikacin dosage was calculated according to the conventional method for all the patients, and the prescribed dose was correct only in 25% (n, 16) of the patients.

Nephrotoxicity was detected in 19% (n, 12) of the patients, but amikacin prescription was discontinued in only 50% (n,6) of them.

Table 3: Drug utilization evaluation data on amikacin prescribed in Nemazee Teaching Hospital (n, 63)

Variable	Number (%)
Indication	
Correct	47 (75)
Incorrect	16 (25)
Dosing method	
Pharmacokinetic dosing	0 (0)
Conventional dosing	63 (100)
Prescribed dose	
Correct	16 (25)
Underdose	18 (28)
Overdose	29 (47)
Route of administration	
Intravenous infusion (30 min)	100 (63)
Nephrotoxicity	12 (19)
Discontinuing amikacin prescription	6 (9.5)
Continuing amikacin prescription	6 (9.5)
Monitoring BUN and S_{cr} before administration	48 (76)
Monitoring S_{cr} every 2-3 d after administration	52 (83)
Controlling culture 48-72 h after administration	8 (13)
Monitoring clinical outcome	
Treatment success	51 (81)
Treatment failure	12 (19)
Continuing amikacin prescription	6 (9.5)
Changing amikacin to alternative antibiotics	4 (6.5)
Increasing the dose of amikacin	2 (3)
Patients needed dose readjustment	36 (57)
Dose readjustment was done	4 (6.5)
Dose readjustment was not done	32 (50.5)
Peak concentration (µg/mL)	
Therapeutic level	24 (38)
Toxic level	6 (9.5)
Subtherapeutic level	33 (52.5)
Trough concentration (µg/mL)	
Therapeutic level	28 (45)
Toxic level	28 (45)
Subtherapeutic level	7 (10)

BUN: Blood urea nitrogen; S_{cr}: Serum creatinine

During amikacin treatment, fever, WBC count, and other related clinical signs and symptoms of infectious diseases were monitored for 89% (n, 56), 63% (n, 40), and 10% (n, 6) of the patients, respectively. According to these parameters, favorable clinical response was observed in 81% (n, 51) of the patients and treatment failure occurred in 19% (n, 12) of the study population. Forty-eight (76%) patients had renal failure. For 12 (19%) patients, the dose of amikacin was adjusted at the start of treatment, and 36 (57%) patients needed dose readjustment, which was done for only 4 (6.5%) patients.

The mean±SD of the peak and trough serum concentrations of amikacin was 15.67±7.79 and 7.63±5.4 µg/mL, respectively. Desired peak and trough concentrations were obtained in 38% (n, 24) and 45% (n, 28) of the patients, respectively. Finally, the mean±SD score of amikacin usage in Nemazee Teaching Hospital was calculated 5.8±0.3 out of 12, meaning that overall adherence of amikacin usage to the guideline was only 48%.

Discussion

The inappropriate use of antimicrobial agents is one of the most important factors inducing microbial resistance.[3] In addition, inappropriate antibiotic prescription can prolong the duration of hospitalization[21,22] and increase patients' mortality rates.[23,24] Previous studies have demonstrated that up to 50% of antibiotics prescriptions in hospitals are inappropriate.[25,26] In our study, the adherence of amikacin usage to the guideline was only 48%. The main faults in the prescription of amikacin were inappropriate dosing method, poor patient monitoring, and ignorance of microbiological data.

The most important defect in amikacin prescription in Nemazee Teaching Hospital was the dosing method of this antibiotic. For all the patients, the dose of amikacin was determined according to the conventional method and the clinicians did not take pharmacokinetic parameters into consideration. Clearly, the pharmacokinetic dosing method can decrease the treatment failure and toxicity of aminoglycosides.[27,28] 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).

Several studies have shown a significant tendency to underdose, which can give rise to undesired peak serum concentrations when the conventional dosing method is used.[27,29]

Franson et al.[27] compared the pharmacokinetic dosing method with the conventional dosing method in a sample of American patients who received aminoglycosides and found that the patients in the pharmacokinetic dosing-method group received a greater dose (5.1±0.29 mg/kg) than did those in the conventional method group (3.3±0.15 mg/kg; P< 0.05) and also achieved a higher peak serum concentration (6.1±0.26 vs. 4.5±0.19 µg/mL; P<0.001). Leehey et al.[29] in their study performed on a sample of the American population found out that the administered aminoglycosides doses in the pharmacist-directed dosing patients (using the

Bayesian method) were significantly higher than those in the physician-directed dosing patients (107±21 vs. 91±26 mg/dose; P<0.001) and that the mean peak serum concentrations were higher in the pharmacist-directed dosing patients as well (5±1.7 vs. 4±1.0 µg/mL; P=0.003).

According to the low therapeutic index of aminoglycosides, the TDM of these antibiotics can reduce their toxicity and improve their efficacy.[30,31] In our study, desired peak concentrations were obtained in only 38% (n, 24) of the patients. In a study by Shrimpton et al.,[6] serum assays were done for 63% of the aminoglycosides courses and all the amikacin concentrations were within the desired therapeutic range. In another study done by Davey et al.,[7] only 82 (32%) of the 225 patients who received aminoglycosides had no interpretable serum assay and in 33 (19%) of the remaining 173 patients, the serum concentrations were within the recommended therapeutic range. Our findings along with other studies support the necessity of the TDM of aminoglycosides, although the TDM of these antibiotics is not performed in Nemazee Teaching Hospital.

Nephrotoxicity and ototoxicity are the most important adverse effects of aminoglycosides.[32] The ototoxicity of amikacin was not studied in this research because audiometry tests should be done in a soundproof room to control background noise and visual disturbance and also it is often impractical to transport some patients due to isolation precaution or the need for supportive medical equipment. Furthermore, the results of clinically conducted audiometry have day-to-day variations because of background changes and may cause a false judgment of amikacin ototoxicity.[14]

Nephrotoxicity was detected in 19% of our patients, which is unacceptable in comparison with the findings in similar studies such as those conducted by Kashuba et al.[33] (10.3%) and Shrimpton et al.[6] (1.1%). The high incidence of nephrotoxicity can be related to poor patient monitoring and also inappropriate dosing method. In this study, for 76% of the patients, S_{cr} and BUN were monitored before amikacin administration and S_{cr} was measured every 2 or 3 days in 83% of the patients.

In the study by Kashuba et al.,[33] S_{cr} concentrations were monitored before aminoglycosides therapy, every 2 days during therapy, and 3 to 5 days after the end of treatment for all the patients.

In several studies, the relationship between aminoglycosides nephrotoxicity and pharmacokinetic dosing was evaluated. In two studies performed in Israel and the United States, it was shown that pharmacokinetic dosing might reduce aminoglycosides nephrotoxicity.[28,34] In contrast, two studies that employed the Bayesian method for aminoglycosides dose adjustment in a sample of the American population concluded that pharmacokinetic dosing did not affect the risk of nephrotoxicity related to aminoglycosides therapy.[29,35]

Although previous studies have shown that antibiotics treatment on the basis of microbiological data can confer more rational treatment, improved clinical outcome, and reduced costs,[36,37] many clinicians ignore these data. In the current study, only in 13% of the patients was amikacin prescribed based on microbiological data. However, in similar studies such as those performed by Shrimpton et al.[6] and Zahar et al.,[38] aminoglycosides were prescribed based on microbiological documents in 45% and 79% of the patients, respectively. Our results showed that the clinicians who prescribed amikacin or other antibiotics in Nemazee Teaching Hospital believed that microbiological tests did not have enough accuracy and precision for antibiotics selection. Therefore, antibiotics therapy was conducted mostly based on the physician's clinical judgment and experience. The indication for amikacin was correct in 75% of our patients, which is nearly similar to the results of a study by Ramesh et al.,[5] who reported that the indication for amikacin was appropriate in 73% of their patients.

In the present study, appropriate response to antibiotics treatment was observed in 81% of the patients. This rate is acceptable in comparison to those reported by previous investigators such as De Maria et al.,[39] who reported that 80% of their patients were cured with aminoglycosides, and Kashuba et al.,[33] who reported that appropriate clinical response was achieved in 92% of their patients. Nonetheless, given the low compatibility of amikacin usage with the guideline, it seemed that this appropriate response was more related to other antibiotics used in combination with amikacin such as β-lactams.

Amikacin was infused over 30 minutes in our patients in accordance with the standard guideline in order to prevent nephrotoxicity and ototoxicity. The result of our study is completely consistent with those of previous other studies.[40,41] Consequently, it seems that our nurses had enough information and were also well-informed about amikacin administration.

Conclusion

The most significant problem of amikacin usage in the Internal Medicine Ward of Nemazee Teaching

Hospital was the lack of knowledge about the substantial role of pharmacokinetics in optimizing amikacin usage. Using pharmacokinetic dosing methods is strongly recommended because these methods can improve clinical outcome by achieving the desired serum concentration while reducing toxicity.

Moreover, the current study showed that the clinicians did not pay enough attention to microbiological data. The prescription of amikacin according to microbiological document can not only improve its efficacy but also reduce the incidence of resistant microorganisms. In addition, performance of population pharmacokinetic studies, implementation of a standard guideline for amikacin usage, presence of clinical pharmacists, and provision of equipment and trained personnel for TDM can improve the safety and efficacy of treatment with amikacin.

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