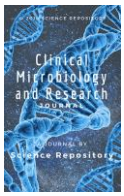

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Research Article

Prescribing Patterns of Aminoglycoside Antibiotics in a Teaching Hospital in Sudan

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ABSTRACT

Background: Aminoglycoside antimicrobials are widely used for the treatment of severe gram-negative bacterial infections. Their inappropriate use may result in treatment failure, development of resistant pathogens, and toxicity. Drug utilization evaluation of aminoglycosides can improve rational use.

Purpose: This study intended to assess the prescribing patterns and potential problems associated with gentamicin and amikacin use.

Methods: This prospective observational study was conducted at Soba University Hospital, Khartoum, Sudan. Patients' demographics, clinical and prescription information were collected using a data collection form. Laboratory data of patients were collected from the patients' files. Ideal body weight was calculated to assess dose appropriateness, and adverse drug reactions were observed.

Results: A total of 200 patients were included in the present study, two-thirds of the patients were prescribed gentamicin, while the remainder were given amikacin. Dosing was inappropriate in (60.6%) and (76.5%) of patients on gentamicin and amikacin respectively. Conventional dosing was used more commonly (67%) than extended dosing (33%). All indications for the use of these drugs were found to be appropriate. In (72%) of cases, both gentamicin and amikacin were prescribed based on microbiological sensitivity testing. Auditory function monitoring was only performed for neonates and infants. Nephrotoxicity was detected in 7 patients (9.3%), and ototoxicity in one patient (1.3%).

Conclusion: Although prescription and dosing based on ideal body weight and microbiological data were reasonably common, higher compliance with recommended practice is needed in addition to therapeutic drug monitoring in order to ensure safe and effective treatment, and reduced antibiotic resistance.

Introduction

Aminoglycoside antimicrobials are widely used for the treatment of severe gram-negative infections, such as hospital-acquired pneumonia and sepsis [1]. Moreover, four decades ago, aminoglycosides were used as monotherapy for Gram-negative sepsis. They were replaced by new generation cephalosporins, carbapenems, and fluoroquinolones which have broad-spectrum activity against gram-negative bacteria and are less toxic than aminoglycosides [2]. Furthermore, aminoglycosides are also used in combination with penicillin for providing synergistic action in the treatment of certain gram-positive infections such as infective endocarditis. The commonly used aminoglycoside antibiotics are gentamicin, tobramycin, netilmicin, and amikacin [1]. Aminoglycoside antibiotics are generally bactericidal and exhibit concentration-dependent bacterial killing in addition to broad-spectrum activity used for both prophylaxis and treatment of infections [3]. They have a narrow therapeutic index and it has been found that ototoxicity and nephrotoxicity are the two main adverse-effects which can limit the clinical utility of aminoglycosides [3-5].

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It is well known that irrational use of antibiotics is one of the major causes of the spread of multidrug-resistant bacteria. Implementation of antibiotic stewardship programs is essential in the control of bacterial resistance [6, 7]. The inappropriate use of aminoglycosides may result in the development of resistant pathogens. Also, aminoglycosides are considered among the most common nephrotoxic and ototoxic drugs in humans [8, 9]. Drug utilization evaluation (DUE) of these antibiotics is necessary to improve their usage [10]. The goal of DUE is to understand how and why drugs are used to promote appropriate use and improve health outcomes [11]. Many studies have been conducted on the DUE of aminoglycosides, in particular, the therapeutic drug monitoring (TDM) of these drugs [10, 12-14]. These studies evaluated the usage pattern of, among other aminoglycosides, gentamicin and amikacin, concerning their indication, dose, duration, safety and cost. There is no standard prescribing protocol available for the prescription and administration of aminoglycosides in the Soba University Hospital. Thus, the present study was undertaken to assess the potential deviations in prescribing and administration of gentamicin and amikacin.

Materials and Methods

A prospective observational study was conducted at Soba University Hospitals, Khartoum, Sudan. In a 2-year period (01 March 2015 to 28 February 2017). The participants included in the study, had the following criteria: (i) Sudanese nationality, (ii) have no allergy to aminoglycosides (iii) had no history of hearing loss or renal impairment. Before enrollment in the study, participants signed an informed consent to participate in the study and receive intravenous aminoglycoside for any relevant therapeutic indication.

The demographic data of the patients were collected using a data collection form, including the patients' age, sex, ideal body weight, date of admission, date of discharge, past medical history, medication history and the diagnosis. Laboratory data of patients were collected from the patients' files including serum creatinine (SCr), blood urea nitrogen (BUN), white blood cell counts (WBC) and results of urinalyses and cultures. Nephrotoxicity and ototoxicity of gentamicin and amikacin, if any, were recorded. Other miscellaneous data was also observed, including body temperature, and signs and symptoms of infectious diseases. Ideal body weight (IBM) rather than actual body weight was used to evaluate dosing appropriateness, as aminoglycosides distribute poorly in adipose tissues. For obese patients (i.e. body mass index >30 kg/m^2, or >120% of ideal body weight), the ideal dose was calculated using the weight obtained from the following formula:
Obese Dosing Body Weight= IBW + 0.4 (ABW–IBW)
Where ABW= Actual Body Weight & IBW =Ideal Body Weight
Ideal body weight:
For males = 50kg + (0.9 kg per cm height over 152 cm)
For females = 45.5kg + (0.9 kg per cm height over 152 cm) [15].

The cochlear function was evaluated in infants and neonates before and after gentamicin and amikacin. Outoacoustic Emission (OAE) test was used to assess ototoxicity. The OAE is a low-level sound emitted by the cochlea either spontaneously or evoked by an auditory stimulus. The test provides information that correlates to the function of the outer hair cells. The distortion product (DP) version of OAEs was used. The tone used was 35db, and the test took about 30 seconds for each ear. The results were set as either passed or referred. Pass means a normal function of the cochlear.

Statistical Analysis

The participants' responses were encoded, and the data were analyzed using Statistical Package for the Social Sciences (SPSS, version 20.0, Chicago, IL, US). A descriptive analysis of the data was undertaken. Continuous variables are presented as means ± standard deviations (SD) and categorical data as percentages (proportions).

Table 1: Study population demographic characteristics and indications for prescribing aminoglycosides.

Characteristic	**Gentamicin (n=132) Number (%)**	**Amikacin (n=68) Number (%)**	**Total (n=200) Number (%)**
Average age (years)	9.86	4.16	7.87
Age groups			
<1 month	34 (25.8%)	46 (67.6%)	80 (40%)
> 1 month and ≤ 24 months	40 (30.3%)	12 (17.6%)	52 (26%)
>24 months and <18 years	41 (31%)	6 (8.8%)	47 (23.5%)
≥18 years	17 (12.9%)	4 (5.9%)	21 (10.5%)
Ideal body weight in kg (Mean ± SD)	16.83±20.4	9.21±18.43	14.24±20
Aminoglycoside prescribed	132 (66.0%)	68 (34.0%)	200 (100.0%)
Indication for aminoglycoside			
Neonatal sepsis			78 (39%)
Infantile sepsis			28 (14%)
Urinary tract infection			26 (13%)
Sepsis			25 (12.5%)
Pneumonia			15 (7.5%)
Infective endocarditis			8 (4%)
Surgical wound infection			7 (3.5%)
Meningitis			6 (3%)
Febrile neutropenia			5 (2.5%)
Diabetic septic foot			2 (1%)

Results

The 200 participants included in the study were male (49%; n=98) and female (51%; n=102) patients. Aminoglycosides were prescribed in the hospital for ten therapeutic indications, the most frequent being neonatal sepsis (39%; n=78), infantile sepsis (14%; n=28) and urinary tract infections (13%; n=26). Most (40%) of the patients included in the DUE were pediatric patients aged less than one month. As shown in (Table 1), two-thirds (66%; n=132) of the patients who were prescribed gentamicin were divided into two groups: (i) patients receiving conventional dosing regimen (three or two times a day) of gentamicin (65.2%; n= 86) and (ii) patients receiving extended (once daily) dosing of gentamicin (34.8%; n=46).

A similar pattern was seen in patients prescribed amikacin (34%; n=68), where it was prescribed to: (i) patients receiving a conventional dosing regimen (70.5%; n=48) and (ii) patients receiving extended dosing regimen (29.5%; n=20). Ideal dosing according to IBW calculations was done for gentamicin (59.8%; n=79) and amikacin (70.5%; n=48). Dosing was appropriate in 60.6% (n=80) of the cases of gentamicin, based on the ideal body weight, (39.4%; n=52) of the patients received a higher dose than ideal daily dose. Lower doses were not prescribed. Out of 34% (n=68) of patients on amikacin, dosing was appropriate in 76.5% (n=52) patients. Inappropriate dosing was most commonly observed among patients who received conventional dosing of gentamicin (35.6%; n=47) and amikacin (13.2%; n=9) (Table 2).

Table 2: Aminoglycosides prescription information. [see above comment on font size]

Aminoglycoside	**Gentamicin Number (%)**	**Amikacin Number (%)**	**Total Number (%)**
Average dose (mg/kg/day)	5.2±1.9	17.7±4.8	N/A
Dose frequency			
Conventional dosing	86 (65.2%)	48 (70.6%)	134 (67%)
Extended dosing	46 (34.8%)	20 (29.4%)	66 (33%)
Dosing based on ideal body weight			
Correct dose	80 (60.6%)	52 (76.5%)	132 (66%)
Incorrect dose (total)	52 (40.2%)	16 (29.4%)	68 (34%)
Over-dosed			
Conventional dosing	47(35.6%)	9 (13.2%)	56(28%)
Extended dosing	5 (3.8%)	1 (1.4%)	6 (3%)
Under-dosed			
Conventional dosing	0 (0%)	3 (4.4%)	3 (1.5%)
Extended dosing	0 (0%)	3 (4.4%)	3 (1.5%)
Duration of therapy			
2 to 5 days	29	5	34
6 to 9 days	46	16	62
10 to 13 days	49	35	84
≥14 days	8	12	20
Mean ± SD	8.28±3.48	9.75±2.78	8.78±3.33
Basis for prescription			
Clinical judgment	46 (34.8%)	10 (14.7%)	56 (28%)
Microbiological sensitivity tests	86 (65.2%)	58 (85.3%)	144 (72%)
Monitoring parameters			
Aminoglycoside blood level	2 (1.5%)	0 (0%)	2 (1%)
Renal function (SCr and BUN)			
Before and after treatment	45 (34.1%)	30 (44.1%)	75 (37.5%)
Only before treatment	66 (50%)	31 (45.6%)	97 (48.5%)
Not done at all	21 (15.9%)	7 (10.3%)	28 (14%)
Incidence of nephrotoxicity	4 (8.8%)	3 (10%)	7 (9.3%)

The mean duration of therapy was 8.28±3.48 days for gentamicin and 9.75±2.78 days for amikacin. In (72%; n=144) of cases aminoglycosides were prescribed based on results of microbiology sensitivity testing. Amikacin was prescribed based on results of microbiology sensitivity testing more frequently than gentamicin (85.3% of cases compared to 65.2%). Nephrotoxicity occurred in (3.5%; n=7) of patients treated with aminoglycosides. The (OAE) test system was used for neonatal hearing screening just after birth, but it was not practiced for testing after aminoglycoside therapy.

Assessment of ototoxicity was done using (OAE) test system for neonates and infants who received gentamicin and amikacin. The duration of treatment showed high significance with ototoxicity (P <0.001). No significant difference between the two groups in demographics, clinical data, and prescription information. In gentamicin group, all patients showed normal results and only one patient (1.3%) developed ototoxicity, while all patients in the amikacin group passed the test.

Discussion

All therapeutic indications for aminoglycosides were found to be appropriate (Table 1). Most patients who received aminoglycosides in our hospital were pediatric patients. This is because neonatal sepsis management guidelines recommend the use of intravenous benzyl penicillin with gentamicin or amikacin as the first-line antibiotic combination for the systemic treatment of suspected infection unless microbiological surveillance data reveal local bacterial resistance patterns indicating the need for a different antibiotic [16, 17]. The recommended dose of gentamicin is 3-5mg/kg/day for conventional dosing, and it may be decreased to 2 mg/kg/day in pediatric patients. The extended dosing regimen for gentamicin doses can reach up to 4-

7mg/kg/day. The recommended dose of amikacin is 15-22.5 mg/kg/day [18, 19]. Gentamicin average dose was (5.2±1.9), while amikacin average dose was (17.7±4.8), which is higher than the recommended doses for each. Since aminoglycosides have limited tissue distribution, a narrow therapeutic index and are eliminated by the kidneys, their administration necessitates careful and appropriate selection of empiric dosing regimens to minimize the development of toxicity [1].

The present study showed a high frequency of inappropriate dosing according to IBW calculations. The most frequently observed form of inappropriate dosing was overdosing with conventional dosing regimens, which may directly cause toxicity [20, 21]. It may be attributed to conventional dosing being the most common method of dosing aminoglycosides in our hospital. There is a strong evidence that once-daily dosing of aminoglycosides increases efficacy and reduces toxicity and cost [22, 23]. In an earlier study in Iran, the average duration of amikacin therapy was 8.8±6 days, which was very close to the average duration of therapy in our study 9.75±2.78 days [12]. Antimicrobial treatment based on microbiological sensitivity data guides rational treatment, which improves treatment outcomes and reduces costs [24, 25]. In the present study, 72% of the patients were given aminoglycosides based on microbiological sensitivity testing. In an audit of prescription and assay of aminoglycosides in a UK teaching hospital, aminoglycosides prescription based on microbiological data was found to be only 45% [26].

Whereas in France, in Henri Mondor Hospital found it to be 79% [27]. TDM of aminoglycosides can decrease the incidence of toxicity and increase efficacy [28]. In comparable studies, even after performing TDM, all concentrations were not found within the desired therapeutic range, and this necessitated dose adjustment [26, 28]. A critical issue concerning the use of aminoglycosides in our hospital is the absence of TDM, a problem that affects many other hospitals in Khartoum. Physicians restrict aminoglycoside use because of their toxicity profile, especially in the absence of TDM capabilities. The development of nephrotoxicity was evaluated in patients who underwent monitoring of renal function before and after aminoglycoside treatment (37.5%; n=75). The incidence of nephrotoxicity (9.3%; n=7) is acceptable as compared to the 10.3% incidence found in a study in the United States [29]. On the contrary, a lower rate of nephrotoxicity (1.1%,) was reported in a teaching hospital in the UK and was considered to be very low relative to the sample size [26]. While in Iran, they found a high incidence of nephrotoxicity (19%), they concluded that it could be related to poor patient monitoring or an inappropriate dosing method [12].

In the present study, only 37.5% of the patients were monitored for Scr and BUN before and after aminoglycoside administration. However, guidelines on the use of aminoglycosides recommend monitoring SCr before initiating aminoglycoside therapy, every 2 to 3 days during therapy and 3 to 5 days after the end of treatment [12, 26, 29]. Most studies in infants and children worldwide demonstrated that hearing loss (Cochlear toxicity) is a rare complication of aminoglycoside therapy in infants and children [22, 23]. Our findings are consistent with these studies: as no nephrotoxicity found in gentamicin in neonates and infant groups. Ototoxicity was found in only one patient (1.3 %) in the gentamicin group, and no ototoxicity has been found in any of amikacin group. The duration of the treatment was 21 days for the single neonate who developed ototoxicity. It has previously been reported that long duration of treatment is responsible for both nephrotoxicity and ototoxicity [30]. In Sudan, the absence of electronic prescription databases hinders the execution of DUE and research. Clinical pharmacists are currently attempting to collaborate with other specialties, and they have started to participate in monitoring drug use as well as developing indicators for drug use evaluation.

Conclusion

In our hospital, aminoglycosides were appropriately prescribed for specific indications. In most cases aminoglycosides were prescribed based on microbiological sensitivity data. However, evaluation of other drug use indicators identified shortcomings in practices and areas for improvement. Aminoglycosides should be dosed based on IBW for all patients. In addition, the use of TDM to guide pharmacokinetic dosing is strongly recommended to increase the likelihood of treatment success and minimize toxicity. This can be done by equipping hospital laboratories with TDM facilities. Moreover, monitoring auditory and renal functions before, during and after treatment should be routinely practiced. The main problem was the lack of knowledge about the substantial role of monitoring serum concentrations of drugs with a narrow therapeutic window.

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Competing Interest

None.

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Ethical Approval

Ethical approval was obtained from the Soba Center for audit and research in Khartoum, Sudan. Institutional Review Board (IRB Number: 10122015).

Highlights

- Conventional dosing regimens were the most common for gentamicin and amikacin, used for 65.2% (n= 86) and 70.5 %(n=48) of patients respectively.
- Ideal body weight calculations were appropriately used to determine the dose for 59.8% of patients on gentamicin and 70.5% on amikacin.
- Inappropriate dosing was most commonly observed among patients who received gentamicin (35.6%) and amikacin (13.2%) by conventional dosing.

- Monitoring blood levels was rarely done (1.5%) of patients on gentamicin and for none of the patients on amikacin).
- Nephrotoxicity occurred in (3.5%) of patients.
- Ototoxicity occurred in one patient only.

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