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Research Article

SIDE EFFECTS MONITORING OF AMINOGLYCOSIDE ANTIBIOTIC IN HOSPITALIZED PATIENTS

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ABSTRACT

Objective: The aim of this study was to monitor the side effects in patients who received aminoglycoside antibiotics at the inpatient service of Fatmawati Hospital from March to May 2017.

Methods: This was an observational study based on data collected through patient interview, prescribing information, and medical records. Data were collected on all inpatients treated with aminoglycosides during the study period (total sampling method). The Naranjo algorithm was used to assess the causality of the observed effects.

Results: The data from 33 patients were evaluated, among whom 14 (42.4%) developed nephrotoxicity and 5 (15.2%) had ototoxicity. Based on the Naranjo algorithm analysis, the five cases of ototoxicity were categorized as probable drug side effects. No correlation was found between any of the side effects and either age (p=0.726) or sex (p=0.620).

Conclusion: In this evaluation of the side effects attributable to aminoglycoside antibiotics in hospitalized patients, nephrotoxicity was the most common, followed by ototoxicity. The latter was deemed probable drug-related side effects based on the Naranjo algorithm. Of the other side effects, twice as many were considered probable as those thought to be possible drug side effects. Neither age nor sex was significantly related to the adverse effects secondary to gentamicin or amikacin.

Keywords: Aminoglycoside, Naranjo algorithm, Nephrotoxicity, Ototoxicity, Side effect.

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INTRODUCTION

Aminoglycoside antibiotics are often used for infectious diseases but may cause serious side effects [1]. Large to scale studies have shown that, among 10,000 adult patients given tobramycin, amikacin, or gentamicin, the incidence of nephrotoxicity ranges from 9.4% to 14%, cochlear toxicity from 6.1% to 13.9%, and vestibular toxicity from 2.8% to 3.5%. In pediatric patients including neonates, 1.6% reportedly had decreased renal function and 2%–2.3% had muscle toxicity [2-5].

Pharmaceutical services guidelines for antibiotic therapy states that the side effects of aminoglycoside antibiotics, particularly nephrotoxicity, necessitate to monitor aminoglycoside side effects of blood drug levels, particularly in patients with underlying renal impairment [6]. Monitoring of aminoglycoside blood drug levels is important because these agents have a narrow therapeutic index, including the commonly used agents gentamicin, amikacin, and tobramycin [7,8].

Given the serious side effects that can be caused by aminoglycosides, practitioners are encouraged to monitor drug side effects including postmarketing monitoring of drugs already approved for use. The Naranjo algorithm was developed to help determine whether a particular adverse effect is likely to have been caused by a drug [9]. This study was undertaken at Fatmawati Hospital, a general hospital and referral center in Jakarta, Indonesia. Monitoring of the side effects of aminoglycoside antibiotics with a narrow therapeutic index had not been widely practiced before this study. Since gentamicin and amikacin were the only two aminoglycosides available in our hospital, this study focuses on those two agents. The purpose of this study was to evaluate the side effects of aminoglycosides prescribed in the hospital.

METHODS

This was an observational prospective cohort study based on data collected from patient interview, prescription information, medical records, and nurses' notes at Fatmawati Hospital from March to May 2017. Records of inpatients aged 1 month and older were included if the patient met the following criteria: (1) Received gentamicin or amikacin for ≥7 days, either as a sole medication or in combination with other antibiotics, (2) had normal serum creatinine levels before aminoglycoside administration (i.e., 0.6–1.5 mg/dL in adults, 0.0–0.9 mg/dL in children), and (3) the patient or a family member was available for interview. The exclusion criteria were the use of other drugs that may increase the side effects of gentamicin or amikacin and incomplete or illegible medical record data.

The data were analyzed with the Naranjo algorithm to assess the causality of adverse events. We assessed the following variables: Sex, age, type of aminoglycoside, dosage regimen, duration of administration, and combinations with other antibiotics. The Chi-square test was used to analyze a possible correlation between age or sex and the incidence of side effects. IBM SPSS Statistics for Windows version 24.0 by IBM Corp. (New York) was used to analyze all the data.

RESULTS

During the study period, 42 patients were treated with an aminoglycoside. We excluded two neonates whose family could not be interviewed and six patients treated with gentamicin or amikacin for <7 days. One another patient died during treatment, leaving 33 patients included in the study. Of these 33, 19 were male and 17 were adults aged 18–60 years. Amikacin was given to 18 patients with a 1 g once daily (30.30% of total patients) dosing regimen for <2 weeks (15 of whom took it for <2 weeks). The most common antibiotic combination was gentamicin with ceftriaxone (36.36% of total patients).

Side effects of gentamicin or amikacin included nephrotoxic, ototoxic, and others. Nephrotoxicity occurred in 14 patients and ototoxicity in 5 (Table 1). All five cases of ototoxicity were categorized by the Naranjo algorithm as probable drug-related side effects (Table 2). Among the other side effects occurring in 15 patients, 10 incidents were considered probable and 5 possible drug side effects.

DISCUSSION

Nephrotoxic side effects

The serum creatinine values were elevated above normal in two patients on amikacin, but in none of the patients treated with gentamicin. Elevated serum creatinine values indicate a decrease in kidney function [6]. Therefore, of the 33 study patients receiving an aminoglycoside, 2 (6.06%) adults possibly had a slight decrease in kidney function.

However, based on the creatinine clearance (Cockcroft-Gault equation), 14 patients (42.4%) had evidence of nephrotoxicity. Among patients receiving amikacin, a 27% decrease in estimated glomerular filtration rate (eGFR) occurred in five patients including two adults and three children. The decrease in eGFR was considered mild to moderate in two adults, moderate to severe in one adult, and severe in one adult. There was no decrease in eGFR in children samples. Among patients on

Table 1: Side effects of gentamicin or amikacin

Category	Adults (n=17) (>18 years)	Children (n=16) (≤18 years)	Total n (%)
Serum creatinine (mg/dL)	Normal (0.6–1.5 mg/dL)	Normal (0.0–0.9 mg/dL)	
Amikacin			
Below normal	4	0	4 (12.12)
Normal	4	8	12 (36.36)
Above normal	2	0	6.06
Gentamicin			
Below normal	2	0	2 (6.06)
Normal	10	3	13 (39.40)
Above normal	0	0	0 (0.00)
Creatinine clearance (mL/min)	Normal (>90 mL/min)		
Amikacin			
>90	4	–5	9 (27.27)
60–89	2	3	5 (15.15)
45–59	2	0	2 (6.06)
30–44	1	0	1 (3.03)
15–29	1	0	1 (3.03)
<15	0	0	0 (0.00)
Gentamicin			
>90	6	4	10 (30.30)
60–89	4	0	0 (12.12)
45–59	0	0	0 (0.00)
30–44	1	0	1 (3.03)
15–29	0	0	0 (0.00)
<15	0	0	0 (0.00)

Table 2: Side effects ototoxicity of gentamicin or amikacin

Side effects ototoxicity	Age category					Total n (%)
	Toddlers	Children	Adolescents	Adults	Elderly	
Amikacin						
Tinnitus	0	0	1	1	0	2 (6.06)
Hearing disorders	0	0	0	0	0	0 (0.00)
Vertigo	0	0	0	0	0	0 (0.00)
Ataxia	0	0	0	0	0	0 (0.00)
Nystagmus	0	0	0	0	0	0 (0.00)
Gentamicin						
Tinnitus	0	0	0	1	0	1 (3.03)
Hearing disorders	0	0	0	0	0	0 (0.00)
Vertigo	0	0	1	1	0	2 (6.06)
Ataxia	0	0	0	0	0	0 (0.00)
Nystagmus	0	0	0	0	0	0 (0.00)
Amikacin						
Drowsiness	0	1	0	1	0	2 (6.06)
Nausea and Vomiting	2	1	0	0	0	3 (9.09)
Headache	0	0	0	0	0	0 (0.00)
Rash	1	0	0	0	0	1 (3.03)
Tremor	0	0	0	0	0	0 (0.00)
Paresthesia	0	0	0	0	0	0 (0.00)
Gentamicin						
Drowsiness	1	0	1	1	0	3 (9.09)
Nausea and vomiting	0	0	1	1	0	2 (6.06)
Headache	0	0	1	1	0	1 (3.03)
Rash	0	0	0	0	0	0 (0.00)
Decreased appetite	0	0	0	0	1	1 (3.03)
Tremor	1	0	0	0	0	1 (3.03)
Paresthesia	0	0	0	1	0	1 (3.03)

gentamicin, there was a 15% decrease in eGFR among four adults, one of whom had a moderate to severe decrease.

The incidence of nephrotoxicity in this study was higher than that found by Overview *et al*. who reported a 10% incidence of aminoglycoside-induced nephrotoxicity [10]. According to the Drug Information Handbook, the incidence of nephrotoxicity ranged from 1% to 10% [8]. By contrast, Pogue *et al*. reported an incidence of aminoglycoside to related nephrotoxicity of 58% among patients in an intensive care unit [11]. Mortality was significantly higher among those with nephrotoxicity than among those without acute renal injury (45% vs. 29%). The wide variation in the results may be due to the differences in the patient populations in each study.

Ototoxic side effects

Ototoxicity occurred in 5 (15.2%) of our patients, three of whom were taking gentamicin. Tinnitus was reported in one adult and vertigo in one adolescent and one adult. Tinnitus occurred with amikacin in one adolescent and one adult.

These findings are in accord with the review by Xie *et al*. They summarized several studies of aminoglycoside treatment of acute infections lasting 5–7 days, indicating that the drugs caused hearing loss in about 20% and loss of balance in 15% [12]. The drug information handbook stated that the incidence of ototoxic events is 1–10% [13]. Ototoxic side effects might also be more likely to occur in the elderly or patients who previously had previously suffered hearing damage [14]. In our study, all the five occurrences of ototoxicity were deemed to be probable side effects of the antibiotics according to the Naranjo algorithm.

Other side effects

Other side effects potentially attributable to aminoglycosides were reported in 15 of the 33 patients (45.5%). These occurred in nine patients treated with gentamicin, including drowsiness in three (one infant, one adolescent, and one adult), nausea and vomiting in two (one adolescent and one adult), headache in one adult, anorexia in one adult, tremors in one infant, and paresthesia in one adult. Among those taking amikacin, six patients experienced other side effects including drowsiness in two (one child and one adult), nausea and vomiting in three (two infants and one child), and rash in one infant.

The incidence of other adverse events in this study was greater than the <1% noted in the drug information handbook [13]. Hypersensitivity reactions are rare except with topical administration with which the incidence is 10% [14]. The difference between the incidence of other side effects in our study and what is reported in the literature may simply be a statistical anomaly due to our small sample size of 33 patients. Among the 15 other effects we observed, 10 were considered probable and 5 possible drug-related effects according to the Naranjo scale.

Based on this research, the result of the Chi-square test between age and side effect stated that 90% of the data had <5 expectation value; thus, likelihood ratio analysis test with significance value (two-sided) was used. 0.726 or >0.05 value was obtained. The results of the Chi-square analysis showed no association between age and side effects attributable to gentamicin or amikacin. Selimoglu stated that among 8333 pediatric patients, 6.0% had nephrotoxicity secondary to an aminoglycoside, although there was no assessment of a relationship between age and the incidence of side effects [15].

The results of the Chi-square test between sex and side effects showed that > 50% of the data had expectation value <5, so Fisher's exact test was used. The analysis indicated no significant relationship between sex and side effects caused by gentamicin or amikacin. Sweileh found a significantly higher incidence of nephrotoxicity among women than men taking amikacin; however, there was no such sex difference for gentamicin-induced nephrotoxicity [16].

CONCLUSION

In this evaluation of the side effects attributable to aminoglycoside antibiotics in hospitalized patients, nephrotoxicity was the most common, followed by ototoxicity. The latter was deemed probable drug-related side effects based on the Naranjo algorithm. Of the other side effects, twice as many were considered probable as those thought to be possible drug side effects. Neither age nor sex was significantly related to the adverse effects secondary to gentamicin or amikacin.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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