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Research Article

Evaluation of Low-Dose Gentamicin Once Daily Dosing Regimen at A General Hospital in Malaysia

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ABSTRACT

Objective: Once daily dosing (ODD) aminoglycoside is gaining wide acceptance as an alternative way of dosing. In our setting it is the regimen of choice whenever gentamicin is indicated. The objective of this study was to evaluate the practice of gentamicin ODD in a public hospital in Malaysia. *Methods*: We conducted a retrospective review of medical records of patients on gentamicin ODD who were admitted to Hospital Melaka during January 2002 until March 2010. All adult patients who were on ODD gentamicin with various level of renal function were included in the study. Patients on gentamicin < 72 hours and pregnant women were excluded. *Results:* From 110 patients, 75 (68.2%) were male and 35 (31.8%) were female. Indications for ODD gentamicin included pneumonia, 34 (31.0%) neutropenic sepsis, 27 (24.5%) and sepsis, 11 (10.0%). The mean dose and duration of gentamicin was 3.2 mg/kg/day and 7 days, respectively. Almost all patients were on gentamicin combined with other antibiotics. Clinical cure based on fever resolution was found in 89.1% of patients treated with ODD. Resolution of fever took an average of 48 hours after initiation of therapy. The evaluation for bacteriologic cure could not be performed because of insufficient data on culture and sensitivity. Out of 38 patients with analyzable serum creatinine data, four patients might have developed nephrotoxicity. *Conclusion:* In our setting, lower dosages of ODD gentamicin when used in combination with other antibiotics seemed to be effective and safe in treating most gram negative infections.

Keywords: once daily dosing; gentamicin; efficacy; low dose.

INTRODUCTION

The unique pharmacokinetic and pharmacodynamic properties of aminoglycosides allow us to improve on the dosage regimen from multiple dosing to once daily dosing (ODD) in selected patients[1]. The efficacy and safety of this ODD regimen have been shown to be better than or as good as multiple dosing[2,3] while other non-clinical benefits include reduction in medical team workload and significant cost saving[4-6]. As a result, ODD regimen has gain wide acceptance[1,7,8] and has been applied even in paediatric patients[9,10].

The exact starting dose used in ODD has not been clearly defined but it is typically equivalent to the sum of doses traditionally used with conventional dosing over a 24-hour period[11]. Most literatures have recommended a dosing range of 5 to 7 mg/kg/day[1,4,12,13]. Dose range of 4 to 6 mg/kg has been used for serious infections and obstetrics and gynecology infections in patients with normal renal function[5,14]. Patients with intraabdominal infections like appendicitis and billiary tract and other gram negative infections have been given 5 to 6 mg/kg[13]. Higher dose up to 7 mg/kg have also been used[4,12]. Despite these recommendations, anecdotal reports have shown that the usual dose used in ODD in our setting was much lower, with an average of 3.5 mg/kg/day. In this study, we evaluated the clinical response of patients treated for various infections on a low-dose gentamicin ODD regimen.

METHODOLOGY

Study Design

This study was conducted at Hospital Melaka, which is a 900-bed government-funded public hospital situated in the state of Melaka, Malaysia. Data were retrospectively collected from the therapeutic drug monitoring (TDM) records of the Pharmacy Department and from patient medical records of the Medical Record Office. The review targeted patients who met the following criteria: (i) admitted to the hospital from January 2002 till March 2010, (ii) adult patients (18 years old and above), and (iii) on gentamicin once daily dosing (ODD) regimen for a duration of at least 72 hours. This study was approved by the Clinical Research Centre of Hospital Melaka and Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-09-381-3940).

Data Collection

Data were collected for (i) patient demographic profile, (ii) indication for gentamicin, (iii) dose and duration of gentamicin, (iv) concurrent antibiotic, (v) length of hospital stay, (vi) culture and sensitivity results, (vii) serum gentamicin concentrations, (viii) white blood count, (ix) body temperature, and (x) serum creatinine. Estimation of creatinine clearance was made using

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Table 1: Baseline Patient Characteristics.

	Number of patient (%)
Gender	
Male	75 (68.2)
Female	35 (31.8)
Age (years)	
Range	44.1-50.8
Mean ± SD	47.4 ±17.9
Weight (kg)	
Range	51.9-59.5
Mean ± SD	55.7 ±20.1
Race	
Malay	77 (70.0)
Chinese	22 (20.0)
Indian	5 (4.5)
Others	6 (5.5)
Concurrent medical problems*:	27 (24.5)
Hypertension	24 (21.8)
Diabetes mellitus	13 (11.8)
Acute myelogenous leukemia	22 (20.0)
Others	
Concurrent medications:	12 (10.9)
Fluconazole	11 (10.0)
Frusemide	8 (7.3)
Diclofenac	3 (2.7)
Antituberculosis	2 (1.8)
Itraconazole	1 (0.9)
Naproxen	1 (0.9)
Etoricoxib	

*One patient may have more than one medical problem.

Cockroft and Gault equation[15]. Data on white blood count measured at least 24 hours before the treatment started and after treatment ended were obtained. Serum gentamicin concentrations were measured by fluorescence polarization immunoassay (Abbott Laboratories, Illinois) and these data were retrieved from TDM records.

Outcomes

Clinical cure was defined as recovery of signs and symptoms of infections such as temperature and white blood count for 72 hours. Failure was defined as persistently elevated temperature or persistence or worsening of signs and symptoms of infections 72 hours after the initiation of therapy. Bacteriological cure was defined as eradication of the original causative organism from the blood and the original infection site[16]. Nephrotoxicity was defined as an increased in the serum creatinine by 0.5mg/dL (~ 45 µmol/L) of its baseline[6,17]. Creatinine clearance > 60 ml/min was considered normal renal function. Length of hospital stay was calculated from those days the patient been hospitalized during gentamicin therapy.

Statistical Analysis

Table 2: Indications of Gentamicin and Organisms Isolated.

	No of patient (%)
Indications	
Pneumonia	34 (31.0)
Neutropenic Sepsis	27 (24.5)
Sepsis	11 (10.0)
Urinary Tract	6 (5.5)
Infection	4 (3.6)
Tuberculosis	3 (2.7)
Abscess	28 (25.5)
Others	
Concurrent antibiotics:	66 (60.0)
Cephalosporins	43 (39.1)
Antibacterial	34 (30.9)
Combination	23 (20.9)
Penicillins	15 (13.6)
Others	11 (10.0)
Carbapenems	11 (10.0)
Macrolides	
Quinolone	
Organism (s) isolated*	
Gram-negative	37 (36.3)
Acinetobacter baumannii	24 (23.5)
Pseudomonas aeruginosa	20 (19.6)
Klebsiella pneumonia	14 (13.7)
Escherichia coli	8 (7.8)
Staph coagulase negative	8 (7.8)
Proteus mirabilis	5 (4.9)
Pseudomonas fluorescens	5 (4.9)
Stenotrophomonas (Xantho) maltophilia	4 (3.9)
Enterobacter cloacae	2 (2.0)
Pseudomonas putida	2 (2.0)
Haemophilus influenza	2 (2.0)
Pseudomonas pikettii	16 (15.7)
Others	15 (14.7)
Gram-positive	3 (2.9)
Staph aureus	2 (2.0)
Staph epidermidis	7 (6.9)
Streptococcus Group D	
Fungus	
Candida sp	

* Percentage calculated based on 102 patients with positive culture; some patients had more than one type of organism isolated.

Descriptive statistics was expressed as mean, percentage and standard deviation. Data were analyzed using PASW Statistics 18 for Windows (IBM, United States).

RESULTS

Demographic and clinical characteristics

Of 214 patients who were on once daily gentamicin regimen from January 2002 till March 2010, 110 patients met the inclusion criteria. 104 patients were excluded (pregnant, n=6; on gentamicin therapy less than 72 hours, n=18; patients who were initially administered with multiple daily dosing, n=47 and age below 18 years old, n=33). Table 1 presents patient characteristics.

The majority of patients (84.4%) had a comorbid condition at the time of hospitalization. Hypertension and diabetes mellitus were the two most common diseases and were present in 24.5% and 21.8% of patients, respectively. Only 68 (61.8%) patients had serum creatinine measured before gentamicin therapy. The distribution of estimated creatinine clearance was: < 20 ml/min (n=3), 20 – 60 ml/min (n=5) and > 60 ml/min (n=60).

Indication

The most frequent indication for gentamicin was pneumonia, diagnosed in 34 (31.0 %) patients (Table 2). 108 (98.2%) patients received concurrent antibiotics. Two patients received gentamicin alone. The most common concurrent antibiotic was cephalosporins (eg. cefepime, cefoperazone, ceftriaxone and ceftazidime), which was used in 66 patients. Antibacterial combinations like cefoperazone-sulbactam, piperacillin-tazobactam, amoxicillin-clavulanic acid and ampicillin-sulbactam were used in 43 patients.

Organisms isolated

Only 102 patients (336 isolates) had data on culture and sensitivity (C&S). Common sources of culture included blood (n=102), urine (n=69), endotracheal tube (n=47) and sputum (n=41). 148 isolates were negative whereas 14 produced mixed growth. *Acinetobacter baumannii* was found in 37 isolates, followed by *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Staph. aureus* and *Escherichia coli*. Gram positive cultures included *Staph aureus*, *Staph epidermidis* and *Streptococcus Group D* (Table 2).

Dose and duration of gentamicin

The lowest dose given was 60 mg daily (n=1) and the highest was 360 mg daily (n=1). The most common doses were 160 mg (n=32) and 240 mg (n=27). The mean dose of gentamicin was 3.2 mg/kg/day and ranged from 2.96 to 3.35 mg/kg/day. The median duration of gentamicin was 7 days (range: 7.07-8.68 days) (Table 3).

Serum concentration

When serum gentamicin was monitored, sampling was done at 1-hour (C1), 6-hour (C6) post dose or just before the next dose (pre concentration). C1 and C6 were monitored in 88 and 43 patients, respectively. Pre-dose concentrations were monitored in 46 patients. Serum concentrations were not monitored in 11 patients during gentamicin therapy.

In patients whom serum concentrations were monitored at C1, the average concentration was found to be 7.40 mg/L (range: 6.71 to 8.08 mg/L). In patients whom C6 were measured, the average concentration was found to be 2.0 mg/L (range: 2.19 to 3.40 mg/L). The average pre dose concentration was found to be 0.75 mg/L (range: 0.76-1.66 mg/L) (Table 3).

Clinical and microbiologic efficacy

A total of 98 (89.1%) patients were afebrile within 72 hours gentamicin therapy. 61 patients had WBC data during therapy and 48 of them (78.7%) had normal WBC. 12 (10.9%) out of 110 patients died due to pneumonia (n=5), sepsis (n=3) and neutropenic sepsis (n=4). The median length of hospital stay was found to be 20 days.

Bacteriologic response could not be evaluated due to lack of culture and sensitivity data after treatment. Post-therapy culture and sensitivity data was available only in 14 (12.7%) patients.

Toxicity

Safety of Gentamicin ODD

None of these patients were evaluated for ototoxicity. 68 (61.8%) patients had serum creatinine measured before gentamicin therapy. Only 38 patients had both serum creatinine before and after treatment. Four patients (10.5%) had serum creatinine increased more than 0.5 mg/dL at the end of gentamicin treatment.

DISCUSSION

In our setting, when gentamicin is indicated for combination therapy with other antibiotics, it is given as once daily dose (i.e. 24-hourly). This administration method has now become a standard treatment regimen for treating most gram-negative infections. As a result, we could not compare the efficacy between ODD and MDD because it was quite difficult to obtain records of patients who were on MDD gentamicin regimen. Earlier, Mardhiah et al reported that 39.3% of therapeutic drug monitoring of gentamicin in this hospital involved ODD regimen. Their study showed only a small percentage of patients (about 20%) was still on multiple daily dose[18]. The conventional way of administering gentamicin as multiple daily has slowly shifted to ODD probably because of the increased awareness among our doctors about its efficacy and safety.

Our study confirms earlier anecdotal reports from local hospitals that doctors were using lower than the recommended doses in the literature. Although the exact reasons for this practice are not known, it has been reported that doctors may base doses on prescription of familiar doses rather than on actual patient parameters[8]. The two most common doses used in our patients were 160 mg and 240 mg, both of which are multiples of 80 mg since gentamicin is available as 80 mg per vial. Such doses also represent the most convenient dose forms to be used.

Nearly 90% of patients were afebrile or had resolution of fever at the end of gentamicin therapy. Unfortunately, data on white blood cell count (WBC) were not always available during therapy. Of those who had WBC monitored during therapy nearly 80% had values in the

Table 3: Treatment Characteristics of Once Daily Dosing Gentamicin.

	Frequency (%)	Mean (SD)	Median (IQR)
Dose			
Dose (mg/kg/day)		3.2 (1.0)	
Initial dose (mg/day)		182 (58)	
Cumulative dose (mg)		1071 (435)	
Treatment duration (day)			7.0 (5.0)
Concentration data			
Peak (mg/L):			
C1 (post 1 hour)		7.4 (3.2)	
Trough (mg/L):			
C6 (post 6 hour)			2.0 (2.9)
C24 (Pre dose)			0.75 (1.1)
Outcome:			
Alive	98 (89.1)		
Died	12 (10.9)		
Length of hospital stay (day)			20 (15.0)

normal range. Similar clinical improvements have been reported with percentage of patients that were clinically cured of more than 85% [19,20]. The majority of patients received combination antibiotics as recommended and this probably contributed to the overall favourable clinical response. Combination antibiotics may produce synergistic antibacterial effects. Bacterial regrowth is suppressed even during gentamicin-free period, because bactericidal activity is maximized by the presence of concomitant antibiotics[21].

Nephrotoxicity is usually the most common adverse effect with gentamicin usage. In our study about 10% of patients might have developed nephrotoxicity as defined by elevation of serum creatinine. Using the same definition of nephrotoxicity, the rate of nephrotoxicity reported varies considerably ranging from 1% to 5%[6,22,23] to as high as 35%[24]. Higher concentration of gentamicin can cause defect to the structure and function of the renal cells[1]. Lower dosage results in lower concentration which may reduce the chances of gentamicin exposure to the renal tubule cells. The risk of nephrotoxicity has also been associated with duration of treatment[25]. In our patients, the median treatment duration was 7 days; this short duration may have contributed to the more favourable outcome. Similarly, other studies where shorter duration of gentamicin was reported, a lower incidence of nephrotoxicity has been reported[21,23,26].

Serum concentration monitoring during gentamicin ODD has been the subject of many discussions[27,28]. Published methods of monitoring like determining a concentration at 6 to 14 hours post-dose are based on specific assumptions like dose, and volume of distribution [4,13]. We are not sure why 6-hour post dose concentrations were monitored in some of our patients. Since patients in this hospital were generally on lower doses than recommended[4,13], this monitoring method may not be suitable in our setting. As expected, the average peak concentration (ie. C1 values) of gentamicin was lower than which had been reported in other studies[17,29,30].

CONCLUSION

In our setting, gentamicin ODD at lower doses when used in combinations with other antibiotics appears to be effective and safe.

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