DEVELOPMENT OF A NOMOGRAM TO GUIDE THE MONITORING OF ONCE DAILY DOSING GENTAMICIN REGIMEN IN HOSPITAL MELAKA

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by

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DEDICATION

To ALLAH SWT

To my husband Rashid Samah
To my sons Adam, Abrisam, 'Ammar and Amirul

And

To my parents and family

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ABSTRAK

Dos sebenar yang digunakan dalam regimen dos gentamisin sekali sehari (ODD) belum dapat ditentukan tetapi ia lazimnya sama dengan jumlah dos untuk 24 jam yang digunakan dalam pendosan konvensional. Namun, kebanyakan literatur mencadangkan julat dos antara 5 hingga 7 mg/kg/hari. Disebalik cadangan ini, ada laporan menunjukkan bahawa dos lazim yang digunakan dalam ODD di negara ini lebih rendah, dengan purata 3.5 mg/kg/hari. Oleh itu, hasilan klinikal dan bakteriologi mungkin berbeza. Sehubungan itu, kaedah pemantauan ODD yang dicadangkan dalam literatur mungkin tidak terpakai dalam situasi tempatan.

Kajian ini dijalankan untuk menilai praktis ODD, untuk menentukan parameter farmakokinetik dan untuk membangun kaedah mudah yang boleh digunakan di Hospital Melaka.

Bahagian pertama kajian ini adalah kajian semula secara retrospektif rekod perubatan pesakit yang menerima rawatan ODD gentamisin di Hospital Melaka. Hasilan yang diukur termasuklah penyembuhan klinikal dan bakteriologi. Bahagian kedua adalah kajian semula secara retrospektif rekod perubatan pesakit untuk menentukan parameter farmakokinetik terpilih drug tersebut. Bahagian ketiga adalah

kajian pemerhatian prospektif dalam pesakit yang diukur kepekatan gentamisin mengikut kaedah persampelan baru. Hasilan yang diukur adalah tempoh tiada drug (DFP). Ujian Anova Satu Hala dan Mann-Whitney digunakan untuk membandingkan parameter farmakokinetik antara kumpulan pesakit sementara korelasi Pearson digunakan untuk menentukan hubungkait.

Dalam Bahagian 1, hasilan klinikal berdasarkan penyembuhan demam didapati dalam 89.1% pesakit yang menerima rawatan ODD. Penilaian hasilan bakteriologi tidak dapat dijalankan kerana data sensitiviti dan kultur tidak mencukupi. Daripada 38 pesakit yang mempunyai data serum creatinine, 4 pesakit mungkin telah mengalami nefrotoksisiti. Dalam bahagian 2, terdapat hubungan yang baik antara pemalar kadar eliminasi, Ke dan umur ($r = -0.453$; $p = 0.001$). Dalam Bahagian 3, Ke yang dikira dari hubungkait ini bersama satu kepekatan darah yang diambil pada 6 jam selepas dos didapati boleh menganggarkan tempoh DFP.

Dalam situasi ini, dos ODD gentamisin yang lebih rendah nampaknya berkesan dan selamat dalam rawatan kebanyakan jangkitan Gram negatif. Umur adalah penganggar Ke yang baik berbanding klearans kreatinin. Pemantauan ODD dalam situasi tempatan boleh menggunakan hanya satu kepekatan darah dan Ke yang dianggarkan tadi, diplot di atas graf yang sesuai untuk menentukan DFP sasaran.

DEVELOPMENT OF A NOMOGRAM TO GUIDE THE MONITORING OF ONCE DAILY DOSING GENTAMICIN REGIMEN IN HOSPITAL MELAKA

ABSTRACT

The exact starting dose used in once daily dosing gentamicin (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. However, most literatures have recommended a dosing range of 5 to 7 mg/kg/day. Despite these recommendations, anecdotal reports have shown that the usual dose used in ODD in Malaysia was much lower, with an average of 3.5 mg/kg. Therefore, clinical and bacteriological cures maybe different. Consequently, published monitoring method of ODD gentamicin in the literature may not be applicable in local setting.

This study was carried out to evaluate the practice of ODD gentamicin, to determine its pharmacokinetic parameters and to develop a simple monitoring method applicable in Hospital Melaka.

Part 1 of this study was a retrospective review of medical records of patients on gentamicin ODD who were admitted to Hospital Melaka. Outcomes measured included clinical and bacteriological cures. Part 2 was also a retrospective review of medical records of patients to determine selected pharmacokinetic parameters of the drug. Part 3 was a prospective observational study in hospitalized adult patients who had serum gentamicin concentrations measured using new sampling strategy. Outcome measured was drug free period (DFP). Oneway Anova and Mann-Whitney tests were used to

compare pharmacokinetic parameters in different group of patients whereas Pearson Correlation was used to determine the relationship.

In Part 1, clinical cure based on fever resolution was found in 89.1% of patients treated with ODD. 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. In Part 2, a good correlation was found between elimination rate constant, Ke and age ($r = -0.453$; $p = 0.001$). In Part 3, Ke calculated from this relationship and a single blood concentration at 6-hour post dose was found to be able to predict the duration of DFP.

In this setting, lower dosages of ODD gentamicin seem to be effective and safe in treating most gram negative infections. Age is a good predictor of Ke compared to creatinine clearance. Monitoring of ODD in local setting can make use of a single blood concentration and predicted Ke, plotted on a suitable graph to determine target DFP.

PART 1. EVALUATION OF THE PRACTICE FOR ONCE DAILY GENTAMICIN USAGE IN HOSPITAL MELAKA.

CHAPTER 1 – INTRODUCTION

1.1 Gentamicin

Gentamicin belongs to the aminoglycoside group. Other commonly used aminoglycoside are tobramycin, amikacin and netilmicin. They have similar physical, chemical, pharmacologic and toxicologic properties. This group of antibiotic has a broad spectrum activity and sensitivity against gram negative bacilli bacteria. It is a bactericidal antibiotic which works by inhibiting protein synthesis of bacteria (Zaske, 1986).

1.2 Toxic Effects of Gentamicin

The most common adverse effects of aminoglycoside are ototoxicity and nephrotoxicity. Both toxicities are related to serum concentrations (Appel and Neu, 1978; Gilbert, 1991; Deamer and Dial, 1996; Mitchell et al., 2005). Other adverse effects of gentamicin are neuromuscular blockade, hypersensitivity, hematologic and central nervous system toxicities (Appel and Neu 1978; Winter, 1996). Neuromuscular blockade is rare and this reaction is more likely to occur when gentamicin is used concurrently with other neuromuscular blocking agents, anesthetic agents or calcium channel blocker (Zaske, 1986; Gilbert, 1991). The mechanism of aminoglycoside induced neuromuscular blockade involves interference with calcium and acetylcholine.

1.2.1 Ototoxicity

Ototoxicity is generally irreversible or partially reversible (Labovitz et a., 1974; Mitra et al., 1997). The mechanism of ototoxicity of gentamicin involves a saturable process where the drug accumulates in the inner ear or renal cortical cells (Ali, 1995; Selimoglu, 2007). Saturable process involves an accumulation of drug and phospholipids within lysosomes. This condition will lead to overloading of lysosomes. Finally, the lysosomes rupture and they release the content of drug concentration into the cytoplasm which can cause cell defect (Maglio et al., 2002). Gentamicin produces free radicals in the inner ear causing permanent damage to sensory cells and neurons. This condition results in permanent hearing loss (Selimoglu, 2007).

Ototoxicity consists of two types of damages which are auditory and vestibular dysfunctions. Damage to the sensory hair cells of organ of Corti and reduction of cochlear ganglion cells will cause auditory dysfunction, while damage to the hair cells of vestibular epithelia will contribute to vestibular dysfunction (Appel and Neu, 1978; Maglio et al., 2002). Studies in experimental animals have shown the dose related damage to the eight cranial nerve (Appel and Neu, 1978). In a study using guinea pigs, Gilbert (1991) found that with the same total daily dose of gentamicin, there was less evidence of cochlear injury in once daily dosing regimen compared to multiple dosing.

Complaints of buzzing, roaring, ringing, fullness in the ears and hearing loss on two or more days during therapy were considered evidenced auditory dysfunction while complaints of headache, dizziness, vertigo, tinnitus or lightheadedness for two or more

days during therapy were considered evidenced vestibular dysfunction (Benjamin et al., 1989; Janknegt, 1993).

There is lack of data available for ototoxicity since it is difficult to monitor in clinical setting. Evaluation of ototoxicity in clinical setting is using either audiograms or otoacoustic emission (OAE). Audiogram is used to test bilateral hearing at 250, 500, 1000, 2000, 4000 and 8000 Hz (Peloquin et al., 2004). OAE hearing test is performed within 48 hours admission and within 1 week of completion of gentamicin therapy. OAE is only a screening test, therefore, any patient with abnormal OAE need to have ototoxicity confirmed with brainstem auditory evoked response (BAER) (Chong et al., 2003).

Lin et al (2011) performed BAER or ABRs (auditory brainstem responses) in guinea pigs by tone burst in a sound attenuated room. The tone bursts were generated by a programmable attenuator (Intelligent Hearing Systems, HIS Smart EP version 3.97, Miami, FL, USA) with stimulus frequency at 1, 2, 4, 8 and 16kHz (Lin et al., 2011). Each ABR threshold was compared with the baseline threshold. Threshold was defined as the lowest intensity at which a clear waveform was visible. After 4 weeks on gentamicin therapy, they reported that the ABR threshold was elevated at 60dB but there were no significant auditory changes found at 1 kHz to 16 kHz.

1.2.2 Nephrotoxicity

The mechanism of nephrotoxicity involves a saturable process. Mechanisms of nephrotoxicity are probably mediated by hydroxyradicals and renal cortical phospholipidosis. Hydroxyradicals are strong mediators which can cause tissue injury. They can react with metal chelator and can cause oxidizing process to most of organic compounds such as polyunsaturated fatty acids. This can lead to cell membrane injury and protein degeneration (Ali, 1995). Gentamicin concentrates in proximal tubule or inner ear cells after drug administration. It accumulates within the lysosomes. It is continuously taken up by the lysosomes during repetitive dosing. This condition contributes to rupture of cell membranes of the lysosomes, therefore, cause cell necrosis and renal failure (Beaucaire, 2000).

Phospholipidosis occurs when there is an inhibition of phospholipase and sphingomyelinase which both are responsible for phospholipid metabolism. Inhibition of Na^+-K^+-ATPase is one of the suggested mechanism where the inhibition of this enzyme leading to nephrotoxicity. Other mechanisms of nephrotoxicity involve thromboxane A_2 and prostaglandins, effect on microsomal protein synthesis, lysosomal injury, mitochondrial injury and vascular factors (Ali, 1995).

Nephrotoxicity can be detected using sensitive endogenous marker such as urinary gelsolin which appears in urine on day 1 of drug treatment. Other sensitive markers are N-acetyl-ß-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), plasminogen activator inhibitor 1 (PAI-1) and neutrophil gelatinase-associated lipocalin (NGAL)

(Ferreira et al., 2011). Serum creatinine is the least sensitive markers of renal injury because it is elevated only after 3 days of drug treatment. Furthermore, its changes are not affected in the presence of mild kidney damage (Ali, 1995; Ferreira et al., 2011). However, in clinical setting, due to its practicality, the most common method for evaluating nephrotoxicity is monitoring for changes in serum creatinine (Labovitz et al., 1974; Prins et al., 1993; Mitra et al., 1997; Chong et al., 2003; Peloquin et al., 2004; Abdel-Bari et al., 2011).

1.2.3 Factors that increase risk of toxicity

Concurrent therapy with other nephrotoxic or ototoxic drugs such as frusemide, cephalosporin, vancomycin and amphotericin B can increase risk of toxicity (Appel and Neu., 1978; Kaloyanides and Pastoriza-Munoz, 1980; Santucci and Krieger, 2000).

Other factors which may increase risk of toxicity are age and duration of treatment. The risk of hearing loss increased by 24% for every 5-year increase of age (Peloquin et al., 2004). Patients which had been treated with longer gentamicin therapy for example 16 days versus 7 days had higher risk of nephrotoxicity (Prins et al., 1993; Paterson et al., 1998; Raveh et al., 2002). Furthermore, patients with lower rate of creatinine clearance (less than 40 ml/min in once daily dosing group) before gentamicin therapy were also at a risk of nephrotoxicity (Prins et al., 1993).

The initial high peak serum concentration was one of the factors that may cause nephrotoxicity especially in elderly (Koo et al., 1996; Bourguignon et al., 2009). In

contrast, other study found that there was no relationship between serum levels and toxicity of gentamicin (Janknegt, 1993). However, consistently higher trough concentration which was over 2 mg/L found to be associated with nephrotoxicity (Zaske, 1986; Beaucaire, 2000).

Other factors such as liver disease and gender can increase the risk of having nephrotoxicity. Liver disease can cause intra-renal vasoconstriction, reduced renal blood flow and increased plasma renin levels. Stimulation of the renin-angiotensin system has been proposed in aminoglycoside-induced nephrotoxicity (Moore et al., 1984).

1.2.4 Methods to reduce toxicity

The concentration of gentamicin is influenced by the frequency of drug administration [ie. once daily dosing (ODD) or multiple daily dosing (MDD)], longer duration of therapy and total administered dose (Kaloyanides and Pastoriza-Munoz, 1980; Freeman et al., 1997; Beauchamp and Labrecque, 2001).

The risk of nephrotoxicity will be greater when the dose of gentamicin is given frequently such as in MDD regimen. In MDD, trough concentration of gentamicin remains at 1-2 ug/ml which may accumulate with time, therefore, increases the risk of toxicity (Zaske., 1986). Although the total single dose of gentamicin in ODD is higher than MDD, it is less frequent dosing results in lower percentage of dose accumulation (Maglio et al., 2002). This longer interval allows the gentamicin concentration being

eliminated from renal tubular and inner ear cells to fall below minimum inhibitory concentration (MIC) within 12 hours.

Ototoxicity and nephrotoxicity can be prevented by shortening the duration of therapy (3 to 5 days) rather than aim for a specific serum concentration of gentamicin. Slowing the rate of infusion from 30 minutes to 60 minutes can prevent ototoxicity in selected patients (Paterson et al., 1998; Raveh et al., 2002; Peloquin et al., 2004; Selimoglu, 2007). Besides, daily monitoring of serum concentrations and sign and symptom of toxicity can reduce risk of serious adverse event (Apple and Neu, 1978).

Avoiding of the concurrent use of other nephrotoxic agent with gentamicin may prevent nephrotoxicity (Janknegt., 1993; Mitchell et al., 2005). Low dose of gentamicin and monitoring of serum concentration frequently will contribute to low incidence of renal toxicity (Bourguignon et al., 2009; Hajkowitz et al., 2010). Furthermore, in special population like elderly, burn, pregnant and critically ill patients are recommended to give dosage individualization rather than administer a fixed dose of gentamicin (Santschi & Papiah, 2000; Conil et al, 2006; Bourguignon et al., 2009; Goncalves-Pereira, 2010).

1.3 Clinical Use of Gentamicin

Despite its toxicities, gentamicin has been widely used for many types of infection such as lower respiratory tract infection, urinary tract infection, bacteremia, intra-abdominal infection, skin & soft tissue infection, liver abscess, cholecystitis, bone infection and

fever with neutropenia (Benjamin et al 1989; Koo et al 1996; Ministry of Health Malaysia, 2008). Gentamicin has also been used as empirical therapy of serious infections such as nosocomial respiratory tract infections, complicated urinary tract infections and complicated intra-abdominal infections caused by Gram negative bacilli (Durante and Mangoni et al., 2009).

The common organisms which are sensitive to gentamicin include Gram negative bacteria like *Pseudomonas sp, Enterobacter sp, Escherichia coli, Klebsiella sp, Serratia sp* and *Proteus sp* (Mitchell et al., 2005) and Gram positive bacteria like *Streptococci, Enterococcus sp, Staphylococcus sp* (Appel and Neu, 1978; Koo et al., 1996; Wiesenfeld and Heine, 1998; Durante and Mangoni et al., 2009; Abdel-Bari et al., 2011).

Several antibiotic groups such as penicillins and cephalosporins have synergistic activities with aminoglycoside. Combination of gentamicin with penicillins to achieve synergy is useful against gram positive organisms (Appel and Neu, 1978). This synergistic activity is achieved by increasing the porosity of bacteria cell wall caused by beta lactam antibiotic, therefore allowing more aminoglycoside penetration into the bacteria. The combination is useful for life-threatening infections such as endocarditis, pneumonia or bacteremia (Appel and Neu, 1978).

1.4 Rationale of Once Daily Dosing of Gentamicin

An alternative way of gentamicin administration and drug dosing has been developed to maximize efficacy and minimize toxicity. Due to its unique pharmacodynamic properties, the conventional dosing of gentamicin have been changed to once daily dosing (ODD) or extended interval aminoglycosides dosing (EIAD) (Mitchell et al., 2005). Other than reduced toxicity and improved efficacy, once daily aminoglycoside dosing has the advantages of more predictable serum concentrations early in therapy (Prins et al., 1995), and reduces medical team workload and cost (Nicolau et al., 1995; Del Priore et al., 1996; Mitra et al., 1997).

As a result, ODD has become a widely accepted practice in United States (Chuck et al., 2000). An increased in EIAD reports of efficacy and toxicity of aminoglycoside also contributes to increased EIAD use (Chuck et al., 2000). In a survey done in Australia specific for cystic fibrosis units, 54% of units were using ODD regimen while multiple dosing was 46% (Phillips and Bell, 2001). In the United States (US), the adoption of EIAD increased to 4-fold since 1993 to 1998 and was due to the involvement of infectious disease specialist/service and pharmacists in patients therapy (Chuck et al., 2000).

1.5 Pharmacodynamic of Aminoglycosides

Once daily dosing (ODD) is based on pharmacodynamic properties of aminoglycosides such as concentration dependent bactericidal activity and postantibiotic effect (Maglio et al., 2002).

1.5.1 Concentration Dependent Bactericidal Activity

Gentamicin binds to the 30S subunit of mitochondrial ribosome of the bacteria. This binding leads to alterations in protein synthesis and causes death of the cell (Appel and Neu, 1978; Lacy et al., 1998; Mitchell et al., 2005).

Bacterial killing activity of gentamicin is increased when high serum concentration is achieved. It is possible to kill all the organisms in the short period of time (based on half life ~3 hours) when the concentration is very high (Lacy et al., 1998). The optimum effect of gentamicin is achieved when the peak concentration (Cmax) to minimum inhibitory concentration (MIC) ratio is 10:1 (Lacy et al., 1998; Maglio et al., 2002; Mitchell et al., 2005). This ratio is generally accepted ratio of peak serum concentration to MIC. The ratio is the major determinant of response to aminoglycoside therapy. This concentration related response is called concentration dependent bactericidal activity.

1.5.2 Postantibiotic Effect (PAE)

Gentamicin still has a bacterial killing effect even though its concentration falls below the MIC. This effect occurs even when the serum concentration of gentamicin is nearly zero (drug free period) for at least 2 hours. This effect is known as postantibiotic effect (PAE) (Mitchell et al., 2005). The mechanism of PAE is not known, however, it may be due to binding of gentamicin (sublethal concentration) to the bacteria ribosome which contributes to subsequent disruption of protein synthesis (Kurt, 1995; Majtanova and Majtan., 2000).

Several factors can influence the presence and duration of PAE. The duration of postantibiotic effect varies depending on the types of pathogen, class and concentration of antibiotic, duration of antimicrobial exposure and combination of antibiotic-pathogen (Lacy et al., 1998; Maglio et al., 2002). For example, in vitro studies shown that PAE against *Pseudomonas aeruginosa* is 1 to 3 hours, while it is only 0.9 to 2 hours for *Enterobacteriaceae*. However, in animal study the PAE for both organisms can go up to 7.5 hours (Maglio et al., 2002). Some literatures state a range of 0.5 to 7.5 hours for aminoglycoside (Gilbert, 1991; Lacy et al., 1998). The PAEs for *Serratia marcescens* when exposed to 2 times or 4 times MIC of gentamicin was 2.7 hours and 5.9 hours, respectively (Majtanova and Majtan, 2000).

It is important to determine the optimum duration of postantibiotic effect to prevent from bacterial regrowth (Lacy et al., 1998; Maglio et al., 2002). The postantibiotic effect is dependent on the presence of neutrophils. PAE is shorter in patients with neutropenia, so that ODD of aminoglycoside alone is not recommended since it can increase the bacterial regrowth. Therefore, neutropenic patients should be given multiple dosing of gentamicin but not single dose (Galloe et al., 1995). The efficacy of once daily dosing is equal to multiple dosing if the gentamicin is combined with cephalosporins (Maglio et al., 2002). In patients with neutropenic, combination ODD aminoglycoside with penicillin have been recommended (Appel and Neu, 1978).

1.5.3 Adaptive Resistance

Adaptive resistance occurs when the drug uptake by the organism is decreased after initial exposure to the drug (Maglio et al., 2002). Resistance increases over a 2-hour period following removal of the antibacterial after the first exposure of gentamicin to *Pseudomonas aeruginosa*. Combining gentamicin with other antibiotics will reduce adaptive resistance in vitro. In other dynamic in vitro study, adaptive resistance was induced during the first 2 hours after the first dose and remained maximal for up to 12 hours following the peak concentration of 8 mg/L (Barclay and Begg, 2001).

There are two major mechanisms of gentamicin resistance. The first mechanism involved the plasmid mediated production of gentamicin altering enzymes which can inactivate the drug. The second mechanism is by decreasing cell permeability to the drug via alteration of the gentamicin cellular transport system. In other words, adaptive resistance relates to down regulation of active transport of the drug into the bacteria (Appel and Neu, 1978; Barclay and Begg, 2001; Mitchell et al., 2005).

During adaptive resistance period, there is no drug uptake via the active transport. This can occur during normal bacteria replication after exposure to gentamicin. Adaptive resistance can be decreased using drug regimens like ODD that allow for the presence of drug free period (ie. drug holiday) (Lacy et al., 1998). After bacteria with adaptive resistance are grown in drug free period, the active transport will work again (Barclay and Begg, 2001).

1.6 Literature Review

1.6.1 Once daily dosing in adult patients

Once daily dosing has been studied in various types of infections, disease and patient population. Many studies have shown the efficacy and safety of once daily dosing. Some studies reported no significant difference between once daily versus multiple daily dosing in terms of efficacy and safety (Benjamin et al., 1989; Galloe et al., 1995; Deamer and Dial, 1996).

As a single dosing, it is important to achieve sufficiently high peak blood concentration to maximize efficacy but at the same time avoid prolonged exposure of high concentration to minimize toxicity (Deamer and Dial, 1996; Xuan et al., 2004). Once daily dosing not only improves the efficacy but prove to have a small reduction (about 30%) in incidence of nephrotoxicity compared to multiple dosing (Barclay et al., 1999).

Some investigators found once daily dosing was equal in efficacy compared to conventional dosing but increase incidence of nephrotoxicity in once daily dosing (Labovitz et al., 1974; Abdel-Bari et al., 2010). Nephrotoxicity has been shown to decrease in patients receiving individualized pharmacokinetic daily dosing compared to those who received fixed daily dosing (Bartal et al., 2003). However, there was no significant difference in efficacy for both groups eventhough higher mortality rate found in individualized pharmacokinetic daily dosing group (Bartal et al., 2003).

Raz et al (1995) studied the efficacy and safety of intravenous gentamicin given once daily dosing versus multiple dosing to adult patients with suspected or documented gram negative infection. In this study they used gentamicin dose of 4.5 mg/kg once daily and 1.5 mg/kg every eight hours. The results from the study showed that clinical cure rate was significantly higher in the once daily group (87.5%) if compared to other group (69.2%). The microbiological cure rate was also better in the once daily group which 31 out of 36 patients were cured. Ototoxicity was present in three of the patients treated eight hourly.

A good clinical response was observed in 91% of patients with serious infections such as respiratory tract infection, urinary tract infection, cholangitis, cholecystitis, endocarditis and bacteraemia in once daily dosing group compared to multiple dosing group with only 78% (Prins et al., 1993). In this study, they administered to the patients intravenous gentamicin 4 mg/kg once daily and 1.33 mg/kg thrice daily. Nephrotoxicity was observed in multiple dosing group which 24% of patients had serum creatinine increased > 45 umol/L from baseline. They concluded that once daily dosing regimen of gentamicin is at least as effective as and is less nephrotoxic than more frequent dosing per day.

1.6.2 Patient with Obstetrics and Gynecology infections

Study done among postpartum endometritis and puerperal infection patients found that once daily gentamicin was as effective and safe as multiple daily dosing (Del Priore et al., 1996; Mitra et al., 1997; Wiesenfeld and Heine, 1998). Dosages of 5 mg/kg once

daily and 1.75 mg/kg thrice daily gentamicin were used to compare the efficacy and safety between the two dosing methods for patients with postpartum endometritis (Del Priore et al., 1996) while for patients with puerperal infection, they used gentamicin 4 mg/kg daily and 1.33 mg/kg three times a day (Mitra et al., 1997). The peak concentration of gentamicin for once daily dosing group in patients with postpartum endometritis was higher than thrice daily dosing. The trough concentration of once daily dosing group was found to be significantly lower compared to thrice daily trough level. No significant difference was found for serum creatinine level in both groups after treatment and no incidence of nephrotoxicity and ototoxicity occurred in both group (Del Priore et al., 1996).

In pelvic inflammatory disease, recommended to combine IV clindamycin 900mg 8 hourly with IV or IM gentamicin 2 mg/kg loading dose followed by maintenance dose of 1.5 mg/kg 8 hourly. However, if the gentamicin MDD is not responding, the regime will change to gentamicin 5 mg/kg once daily. From the study, they found that ODD was at least as efficacious as MDD without increase risk of toxicity. Furthermore, ODD found to be cost effective in most gynecology infections such as postpartum endometritis and in pregnant women with chorioamnionitis (Ward and Theiler, 2009).

1.6.3 Patients with neutropenia

The efficacy of once daily gentamicin in patients with neutropenia still has to be proved by many clinical studies since the postantibiotic effect is dependent on the presence of neutrophils. Galloe et al (1995) used IV gentamicin 240 mg (3.43 mg/kg) 24 hourly

versus 80 mg (1.14 mg/kg) 8 hourly in neutropenic patients. ODD group had a 2.7% higher cure rate than MDD but the result was not significant. This study found no clinical difference in cure rate between ODD and MDD. However, they recommended that patient with neutropenia should be given multiple dosing of gentamicin instead of once daily dosing (Galloe et al., 1995). The drug free period was shorter in patients with neutropenia, so that once daily dosing of aminoglycoside alone is not recommended since it will decrease susceptibility of organism towards the drug (Maglio et al., 2002).

Neutropenic patients were included in one study of gentamicin in combination with azlocillin for empirical therapy of febrile neutropenic patients following intensive chemotherapy. This study compared the clinical efficacy and safety between ODD and MDD. The dose of gentamicin was 7 mg/kg/day for ODD group and 80 mg 8 hourly for MDD group. 52.0% of patients in ODD therapy were cured and complete resolution of fever compared to 18.5% of patients in MDD therapy. Percentage of failure to resolve in ODD versus MDD was 48.0% and 81.5% respectively. 3 patients in ODD group developed toxicity and only 1 patient in MDD group had mild nephrotoxicity (El Bakri et al., 2000).

The regimen of gentamicin ODD with combination with other antibiotics such as imipenem, piperacillin-tazobactam and cefepime was effective and safe to be used in patients with febrile neutropenia. A recent review by Stabler and Ensom (2011) based on studies assessing the use of ODD in patients with febrile neutropenia shows that the clinical efficacy and safety of ODD was similar to MDD (Stabler and Ensom, 2011).

1.6.4 Critically ill patients

In critically ill patients, there was no significant different between once daily dosing and multiple daily dosing group in terms of clinical and antibacterial efficacy or incidence of nephrotoxicity (Abdel-Bari et al., 2011). The dose of gentamicin given to patients was 240 mg (3.75 mg/kg) once daily and 80 mg (1.32 mg/kg) three times daily intravenously. In this study most of the patients had multiple infections which were pneumonia, abdominal, urinary tract, skin tissue and suspected bacterial infection. 33.3% and 44.4% of patients achieved favorable clinical response in once daily dosing and multiple daily dosing groups, respectively. 17.4% of patients with once daily treatment developed nephrotoxicity while in other group were 15.4%.

1.6.5 Once daily dosing in elderly

Once daily dosing in elderly was found to be equally effective as pharmacokinetic dosing. Koo et al (1996) used a dose of 4 mg/kg/day gentamicin. There was no significant different between two groups in term of bacteriologic and clinical efficacy. Nephrotoxicity occur in 24% of patients in ODD group compared to 14% in the pharmacokinetic dosing group. However, this result was not statistically significant. On the other hand, the incidence of nephrotoxicity was significantly correlated with initial and maximum serum peak concentration in once daily group with a gradual rise of serum creatinine from 0.2 to 0.3 mg/dL.

Nephrotoxicity is always a concern when using aminoglycoside in elderly patients, who may already have poor renal function. Other study among elderly population given a

mean dose aminoglycoside of 1.3 mg ± 0.6 higher than optimal dose showed a significant correlation between high trough concentrations of aminoglycoside with renal damage. Optimal dose was calculated by using ideal bodyweight (IBW) if weight index (actual weight/ideal weight) was > 1 whereas if weight index was ≤ 1, the optimal dose was calculated by using actual bodyweight. The high trough concentration was associated with decreased clearance with advanced age. They also recommended for appropriate weight of the patients because weight from eye-estimation can cause inappropriate dosing, thus can contribute to nephrotoxicity in elderly (Raveh et al., 2002).

Paterson et al (1998) found that in elderly more than 70 years old who received 4 mg/kg gentamicin or tobramycin once daily, 26% of patients with baseline creatinine level of 1.7 mg/dL or greater developed nephotoxicity compared to 12% of patients with baseline creatinine level less than 1.7 mg/dL. They also found that the duration of therapy more than 7 days, concomitant use of allopurinol, baseline creatinine level and hypotension during aminoglycoside therapy were significantly associated with nephrotoxicity.

In elderly patients with creatinine clearance > 60 ml/min, ODD regimen gives better result in efficacy and toxicity (Bourguignon et al., 2009). This study used 3 types of gentamicin dosages which were 1 mg/kg every 8 hours, then 1 mg/kg at various intervals of time and 3 mg/kg once daily. All regimens were for 5 days. For multiple dosing regimens, the dose was effective but there was a significant toxicity occurs after

5 days treatment, regardless of renal function. ODD therapy achieve target Cmax/MIC ratio compared to MDD therapy. Moreover, in ODD, 11.7% of patients had trough level > 2 mg/L compared to 17.3% in MDD. They suggested ODD is not suitable for elderly with baseline creatinine clearance < 60 ml/min because the incidence of nephrotoxicity is above 25%. Therefore, this population need individualized dosing and frequent monitoring of serum concentration (Bourguignon et al., 2009).

The use of ODD gentamicin in elderly is as effective as MDD, however, ODD may increase risk of nephrotoxicity in this population. To reduce risk of nephrotoxicity in elderly patients with ODD, a lower doses of less than 5 mg/kg/day gentamicin can be used and monitoring of serum concentration regularly during therapy.

1.6.6 Once daily dosing in pediatric patients

Recently, many ODD studies were reported in pediatric population including newborns. Pediatric patients have different characteristics compared to adult. Hayani et al (1997) studied comparison between ODD versus MDD regime in neonates. All patients received a dose of 5 mg/kg/day gentamicin to treat sepsis or focal bacterial infection. For MDD dosing the dose given was 2.5 mg/kg twice daily. ODD and MDD groups achieved peak concentration of 10.7 mg/L and 6.6 mg/L respectively. None of the patients developed nephrotoxicity. Once daily gentamicin produces peak concentration greater than multiple dosing which might contribute to greater clinical efficacy in this group.

In a study among infants using dose of 4 mg/kg/day gentamicin, Agarwal et al (2002) found that none of the infants in once daily group had trough concentration < 5 mg/L at 24 hours and 48 hours. However, there was no difference between trough concentration for both dosing methods and no nephrotoxic effects were found in any group.

Hagen et al (2009) compared gentamicin 4 mg/kg/day versus 2.5 mg/kg twice daily in newborns with sepsis. All patients were also on concomitant use with penicillins. Most patients achieved serum concentration > 10 mg/L in ODD group whereas in the MDD group had lower peak concentration. The trough concentration was significantly lower in ODD group which reduce risk of renal toxicity in newborns. They suggested that ODD has potential to increase efficacy and the same time to reduce toxicity.

Serane et al (2009) recommended a dose of 4 mg/kg/day for term babies but not appropriate for neonates between 32 and 36 weeks of gestation because this dose produces serum concentration of gentamicin above the therapeutic range. 33.8% of neonates between 32 and 36 weeks gestation and 24.0% of neonates with ≥ 37 weeks gestation had peak concentration > 10 mg/L, respectively. Furthermore, percentage of neonates with trough concentration > 2 mg/L also higher for 32 to 36 weeks gestation compared to ≥ 37 weeks gestation 21.5% versus 2%.

Once daily gentamicin can be safely used in children and neonates and it has an equal efficacy and safety compared to multiple dosing (Hayani et al., 1997; Chong et al., 2003). The efficacy was greater because ODD produced higher peak concentration and

at the same time reduced the risk of nephrotoxicity with a lower trough concentration. However, dose of gentamicin may be not appropriate in preterm population because can produced higher peak and trough concentration which lead to gentamicin toxicity. Therefore, the interval of gentamicin needs to be prolonged to 48 hours in such patients.

1.7 Problem statement and rationale of the study

The practice of once daily dosing of gentamicin in Hospital Melaka started in 2002. Previously gentamicin has been administered as twice or three times daily. Mardhiah et al (2006) reported ODD gentamicin in Hospital Melaka was practiced in 39.3% of cases compared to 60.7% for MDD. However, the study did not report any clinical outcome associated with ODD used.

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 (Marra et al., 1996). Most literatures have recommended a dosing range of 5 to 7 mg/kg/day (Barclay et al., 1995; Nicolau et al., 1995; Anaizi, 1997; Maglio et al., 2002). 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 (Janknegt, 1993; Del Priore et al., 1996; Wiesenfeld and Heine, 1998). Patients with intraabdominal infections like appendicitis and billiary tract and other gram negative infections have been given 5 to 6 mg/kg (de Vries et al., 1990; Anaizi, 1997). Higher dose up to 7 mg/kg have also been used (Nicolau et al., 1995; Barclay et al., 1995).

Despite these recommendations, anecdotal reports have shown that the usual dose used in ODD in local setting was much lower, with an average of 3.5 mg/kg (Yam and Ab Rahman, 2002; Bala et al., 2005). Therefore, clinical and bacteriological cures maybe different. Moreover, the toxicity events maybe lower with the use of lower dosage of gentamicin. Therefore, we conducted this study to evaluate the practice of ODD therapy in this hospital.

1.8 Objectives of the study

1.8.1 General objective

The general objective of the study was to evaluate the practice and outcome of once daily gentamicin in Hospital Melaka.

1.8.2 Specific objectives

1. To determine indication and dose used for ODD regimen.
2. To evaluate clinical efficacy and toxicity.
3. To determine the practice of serum concentration monitoring for ODD regimen.

CHAPTER 2 – MATERIALS AND METHODS

2.1 Study Design

This study was conducted as cross-sectional study in the Therapeutic Drug Monitoring Unit, Pharmacy Department and Medical Record Office, Hospital Melaka. Data were retrospectively collected based on Therapeutic Drug Monitoring (TDM) records and medical record of patients who were admitted to the hospital from January 2002 till March 2010. This study was approved by Clinical Research Centre (CRC) and Medical Research Ethics Committee (MREC), Ministry of Health, Malaysia. (NMRR-09-381-3940).

Previously, the monitoring of serum gentamicin concentration was to use trough and peak which was C_{24} (concentration at 24-hour post dose) and C_1 (concentration at 1-hour post dose), respectively. Since 2005, when serum gentamicin is monitored, sampling is done at 1-hour (C_1) or 6-hour (C_6) post dose.

2.2 Population and Sample

Sample size was determined by using a single proportion formula $n = [z / \Delta]^2 p (1-p)$ (Naing, 2009) where z (confidence interval) = 1.96 for 95% confidence, p (proportion of outcome in the population obtained from literature) = 39.3% for gentamicin (Mardhiah et al., 2006) and Δ (expected detectable difference between findings from literature and this study) = ± 10%. Therefore, the sample of 91 patients required at the

analysis stage. Sample was selected according to the fulfillment of inclusion and exclusion criteria and the availability of patient's medical records.

2.2.1 Inclusion criteria

All hospitalized adult patients (18 years old and above) who were on gentamicin once daily for at least 72 hours regimen regardless of level of renal function were included in the study.

2.2.2 Exclusion criteria

Patients with gentamicin once daily less than 72 hours, multiple daily dosing, critically ill and pregnant women were excluded because these population might have altered pharmacokinetic parameters.

2.3 Data Collection

The list of patients on gentamicin was obtained from clinical pharmacist monitoring form and TDM record book. The following data were retrieved from patient's medical record. 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.