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Research Article

AUC/MIC RATIO AS A TOOL IN DETERMINING EFFECTIVENESS OF GARASENT® FOR THE PREVENTION OF EARLY ONSET SEPSIS IN HOSPITALIZED NEONATES

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ABSTRACT

Objectives: To evaluate AUC/MIC ratio as a tool in determining effectiveness of Garasent® (gentamicin) as a combination therapy for suspected early onset sepsis (EOS).

Methods: This is a cross-sectional study on neonates in Hospital Raja Permaisuri Bainun Ipoh, Malaysia. The study reviewed records of neonatal patients cases admitted within their 72 hours of life and prescribed with gentamicin combination therapy for suspected EOS. Ratio of area under the curve (AUC) to minimum inhibitory concentration (MIC) of *Klebsiella pneumoniae* and *Coagulase-negative staphylococci* (CoNS) was used to determine effectiveness between AUC groups. MIC for both organisms was set at 1mg/L.

Results/Discussion: Hundred and twenty cases met the inclusion criteria and pharmacokinetics parameters of gentamicin were calculated. Gentamicin was combined with C-penicillin (n=119) or ampicillin (n=1) with mean dose of 4mg/kg q 24-48h and majority was started within 24h of life. Cases were divided into two different AUC group, group 1 <100mg/L/h (n=54) and group 2 >100 mg/L/h (n=66). Ratio of average AUC/MIC was 72 and 135 in group 1 and group 2 respectively. There was no significant difference in term of gender and race between groups (p>0.05). Group 1 has higher mean of birth weight and gestational age and shorter length of stay but it was statistically insignificant. Both groups show 100% treatment successful rate with median treatment duration of 3 days. However, group 2 showed higher numbers of above normal trough (>1µg/ml) and peak (>10µg/ml) concentrations associated with increased risk of toxicity.

Conclusions: AUC/MIC ratio is not a determinant to associate Garasent® effectiveness in the prevention EOS. However, higher AUC/MIC ratio can potentially increase the risk of toxicity.

Keywords: Early onset sepsis, Neonates, Gentamicin, AUC

INTRODUCTION

Garasent ® is the gentamicin injection dosage form used in all Government Hospitals in Malaysia. Gentamicin is the second most common reported medications in Neonatal Intensive Care Unit (NICU) [1]. It is widely used in the treatment of suspected early onset sepsis (EOS) with combination of β-lactam antibiotics especially crystalline penicillin and ampicillin. Gentamicin will provide synergistic activity against the most common pathogens isolated in EOS (eg. *Klebsiella pneumoniae* and *Coagulase-negative staphylococci*)[2-4].

It is very important to monitor and maintain serum gentamicin concentration within the accepted therapeutic range. This is to ensure effectiveness and to minimize possible toxicity effect such as nephrotoxicity and ototoxicity [5]. Knowledge on pharmacokinetics are essential to optimize gentamicin dose especially peak serum concentration monitoring [6-7].

Toxicity is more likely to occur after repeated exposure and prolonged courses of therapy [6]. Gentamicin trough (pre) concentration higher than 2 mcg/ml is strongly associated with toxicity and peak (post) concentration less than 5 mcg/ml is associated with low efficacy [8]. The pre and post sample can be monitored at day 2 of life for dosing adjustment [9].

However, it is difficult to relate gentamicin dose and serum concentration to clinical or bacteriological outcome because antibiotic exposure at site of infection will be modified by tissue penetration and bacteria susceptibility and serum concentration may not predict extra vascular concentration that may be more relevant for the infection site [10]. Even though pharmacokinetics parameters such as maximum concentration (Cmax), minimum concentration (Cmin) and area under the curve (AUC) are good predictors of outcome however, determining pharmacodynamics activities of the antibiotics are still the best.

Gentamicin demonstrated concentration dependant killing effect against gram negative bacteria has been reported by previous studies [11]. With those properties, AUC to minimum inhibitory concentration (MIC) ratio and peak/MIC ratio becomes important predictors to assess gentamicin clinical outcomes [12]. This study was conducted to evaluate AUC/MIC ratio as a tool in determining effectiveness of gentamicin as a combination therapy for suspected EOS.

PATIENTS AND METHODS

This study was approved by Clinical Research Centre of the Ministry of Health (NMRR-11-975-10283) and Research Ethics Committee UiTM (600-RMI (5/1/6/01)). Gentamicin therapeutic drug monitoring (TDM) data were retrospectively collected of neonates admitted in neonatal intensive care unit (NICU) between January 2011 and February 2012 at Hospital Raja Permaisuri Bainun Ipoh and received gentamicin (Garasent®) within 72 hours of life for prevention early onset sepsis.

Data collection

The dosing history and blood sampling time of each neonate was documented. All serum gentamicin concentrations had been analyzed in the Department of Pharmacy, Hospital Raja Permaisuri Bainun, using an automated chemistry analyzer (Siemens, Dade Behring). Neonates who had incomplete history and TDM results were excluded from the study.

Pharmacokinetic and pharmacodynamic analysis

Pre concentration was set at concentration less than 1 mcg/ml as recommended in BNF for Children 2009 [17] and Frank Shann Drug Dose 2008 [18]. Post concentration was set at range of 5-10 mcg/ml and is based on minimum inhibitory concentration (MIC) of two of the most common microorganism isolated in this study, i.e. CoNS and Klebsiella pneumonia where the quoted MIC is 1 mcg/ml [13-14].

Standard pharmacokinetic calculations formula was used to calculate pharmacokinetics parameters (Appendix 1). In this study, AUC is defined as the area of which antibiotic concentrations remain above the target MIC during any one dosing interval (eg. 24 h, 36 h, etc.). MIC is defined as concentrations of antibiotic that are necessary to inhibit bacterial activity. The pharmacodynamic parameter, AUC/MIC ratios were calculated based on MIC 1mcg/ml [13-14]. Cases were divided into two different AUC group, group 1 = AUC <100 mg·h/L (AUC/MIC ratio <100) which increase emergence of antibiotic resistance and group 2 = AUC ≥100 mg·h/L (AUC/MIC ratio≥100) which less emergence of antibiotic resistance [10].

Statistical analysis

All data were entered on a SPSS for windows version 16. The frequencies, percentages, median, quartile, mean and standard deviation of each continuous variable studied was calculated and presented in the form of table and chart. Categorical variables were assessed using Pearson Chi-Square test (χ^2test) or Fisher's exact test and continuous variables were with Mann-Whitney test. For all statistical analyses, the significance was set at 0.05.

Treatment success

Treatment success was considered as the reverse of treatment failure. Treatment failure was evaluated by including cases that required antibiotic(s) substitution within 72 hours due to conditions such as patients who showed no improvement or deteriorating, meningitis or suspicion of meningitis, necrotizing enterocolitis (NEC) or suspicion of other abdominal infection, microorganism resistant to antibiotic and death in 7 days of life due to sepsis.

Two hundred and sixty two Garasent®cases were reviewed and only 153 had therapeutic drug monitoring measurement. Of these, 120 eligible cases were selected and further divided into group of those AUC/MIC ratio <100 (Group 1) and AUC/MIC ratio ≥100 (Group 2).

Table 1: Demographic characteristics

Description	AUC/MIC ratio <100 n=54 (Group 1)	AUC/MIC ratio ≥100 n=66 (Group 2)	*p*
Gestational age (weeks), mean (±SD)	36.74 (3.07)	34.67 (3.29)	0.450
Birth weight (kg), mean (±SD)	2.54 (0.72)	2.17 (0.64)	0.340
Gender			0.260
Male, n (%)	28 (51.90)	41 (62.10)	
Female, n (%)	26 (48.10)	25 (37.90)	
Ethnics			0.190
Malay, n (%)	32 (59.30)	42 (63.60)	
Chinese, n (%)	7 (13.00)	14 (21.20)	
Indian, n (%)	7 (13.00)	7 (10.60)	
Others, n (%)	8 (14.80)	3 (4.50)	
Length of stay (days), mean (±SD)	9.67 (7.71)	13.86 (10.74)	0.320

Table 1 shows the demographic characteristics of Group 1 and Group 2 patients. There was no significant difference between both group in terms of gestational age, birth weight, gender, ethnics and length of hospital stay.

Group 1 patients can be summarised as nearly term neonates with normal birth weight whereas Group 2 patients were premature neonates with low birth weight and required longer hospital stay. More than half of the cases were Malay followed by Chinese and Indian. Gender distribution was equal in Group 1 but in Group 2 more than 60% neonates was male.

Gentamicin dosage

Most of the neonates received 4-5mg/kg gentamicin every 24 to 36 hour (Table 2). However, there were significant differences in the administered gentamicin dose and dosing interval. More of Group 2 patients had received a dose of 5mg/kg dose as compared to Group 1. The majority of Group 1 patients had been administered with a 24 hour regimen while, Group 2 patients had almost similar number prescribed with either 24 hourly or 36 hourly dosing.

Therapeutic drug monitoring

Group 2 had higher incidence of both trough and peak level above recommended concentrations compared to none in Group 1. More than 50% of Group 1 achieved therapeutic range. Around 40% of both groups showed pre level above recommended concentrations (Fig. 1).

Pharmacokinetics parameter

Group 2 had mean pre and post concentration higher than the targeted concentration whereas Group 1 had both mean pre and post concentration in the therapeutic range. Pharmacokinetics profile shows that Group 2 had longer half life and less genamicin clearance while Group 1 had larger volume of distribution (Table 3).

Treatment outcome

Both groups shows 100% treatment success. Only 10% of each groups required substitution of antibiotic within 72 hours post antibiotic exposure. However, none were classified as treatment failure.

Table 2: Gentamicin dose and dosing interval

Description	AUC/MIC ratio <100 n=54 (Group 1), n (%)	AUC/MIC ratio ≥100 n=66 (Group 2), n (%)	*p*
Dose			0.003
4mg/kg	48 (88.89)	43 (65.15)	
5mg/kg	6 (11.11)	23 (34.85)	
Dosing interval			0.003
24 h	40 (74.07)	31 (46.97)	
36 h	14 (25.93)	33 (50.00)	
48 h	0 (0.00)	2 (3.03)	

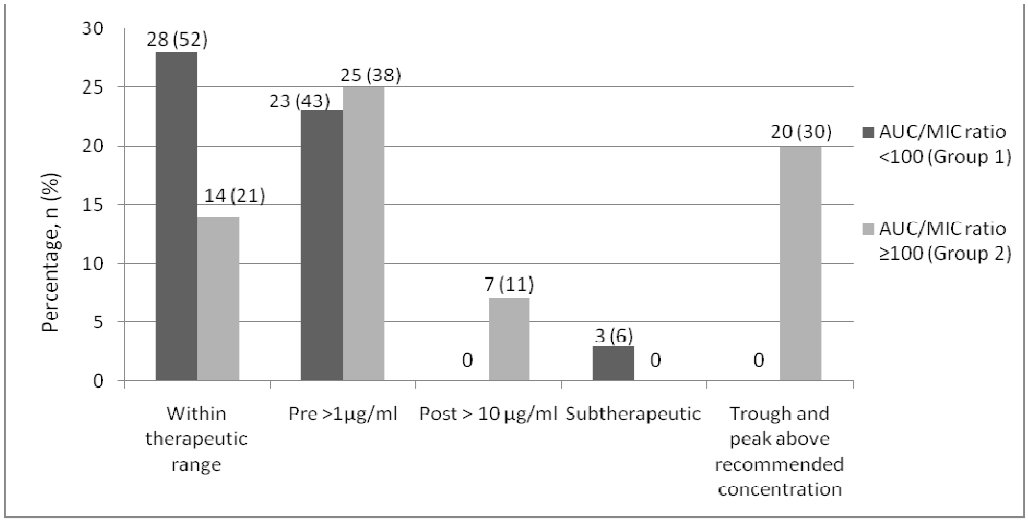

Fig. 1: Gentamicin therapeutic drug monitoring results.

Table 3: Gentamicin pharmacokinetics parameter

Pharmacokinetics parameter	AUC/MIC ratio <100 n=54 (Group 1), mean (±SD)	AUC/MIC ratio ≥100 n=66 (Group 2), mean (±SD)
Pre (µg/ml)	0.90 (0.58)	1.42 (0.64)
Post (µg/ml)	6.42 (2.08)	10.68 (3.01)
Ke (hr^{-1})	0.08 (0.04)	0.07 (0.02)
$T_{1/2}$ (hr)	9.99 (5.09)	10.32 (2.78)
Vd (L/kg)	2.11 (1.09)	1.03 (0.43)
CL (L/kg/hr)	0.16 (0.07)	0.07 (0.03)
AUC (mg · hr/L)	72.10 (17.10)	135.17 (29.41)

Table 4: Treatment outcome

Treatment outcome	AUC/MIC ratio <100 n=54 (Group 1)	AUC/MIC ratio ≥100 n=66 (Group 2)
Duration of treatment (days), median (IQR)	3 (2)	3 (1)
Treatment success, n (%)	54 (100.00)	66 (100.00)
Changes of antibiotic		
None, n (%)	29 (53.70)	23 (34.80)
Within 72h, n (%)	6 (11.10)	6 (9.10)
After 72h, n (%)	19 (35.20)	37 (56.10)
Reasons for changes in 72h		
Optimize/ reduce dose, n (%)	2 (3.70)	2 (3.03)
Renal impairment, n (%)	3 (5.56)	4 (6.06)
Negative culture and sensitivity, n (%)	1 (1.85)	0 (0.00)

DISCUSSION

Gentamicin was commonly used in preventing early onset sepsis (EOS) with combination of β-lactam antibiotics [1]. It will provide synergistic activity against the most common pathogens isolated in EOS [16]. Similar practice can be observed in NICU Hospital Raja Permaisuri Bainun (HRPB).

Recent studies shows extended interval dosing of gentamicin with 4-5mg/kg dose was effective in neonates [23-26]and this concept has been applied by the neonatology physician in this facility. However, there were multiple factors such as gestational age, postnatal age, birth weight, and renal function that will affect the drug concentration [27-29].

Therapeutic drug monitoring for gentamicin is routinely practice to optimise therapy and ensure the safety. Currently, pharmacokinetic parameters such as the elimination rate constant and volume of distribution are used to evaluate gentamicin effectiveness. However, it is insufficient to assess pharmacokinetics parameter alone without correlating with clinical effects (eg. MIC) to ensure effectiveness especially in concentration-dependent killing effect antibiotics [11].

Gentamicin is one of the concentration-dependent killing antibiotic and pharmacodynamic parameters such as peak/MIC ratio and AUC/MIC ratio were the best predictors to evaluate effectiveness because both predictors will correlates drug concentration with clinical effect [12]. There is strong evidence suggesting that by achieving pharmacodynamic target early it may shorten the duration of therapy [20]thus reduce the risk of nephrotoxicity [6].

Total drug exposure which is AUC was more important than peak concentration in determining the drug effectiveness because even though the peak concentration was lower especially in premature neonates but, bacterial killing effect was higher as compared to term neonates [21]. This study observed that premature babies with an average gestational age less than 35 weeks have higher AUC/MIC ratio as compared to nearly term (~37 weeks) babies. It was

consistant with other pharmacokinetic parameters findings and from literatures where premature babies have longer gentamicin half life and less clearance compared with nearly term babie [27-29] due to organ immaturity [3,30].

Previous study reported that AUC/MIC ratio of < 100 was associated with the emergence of resistance in an intensive care unit pneumonia [10].This study showed no such incidences and both groups had good treatment outcome in prevention EOS with 100% successful rate. This findings showed that AUC/MIC ratio is not a significant predictor to associate gentamicin effectiveness in prevention EOS and this outcome could have been influence by the shorter treatment duration (~3 days) set in this study.

Study outcome also suggested that by achieving AUC/MIC ratio above 100 may increase the risk of toxicity with reported mean for both pre and post concentrations above recommended concentration. However, previous documented data showed that nephrotoxicity effect only will be obsereved in multiple dosing per day but not in once-daily dosing when AUC above 100 mg · hr/L and it is predicted to occur when AUC exceeded 700 mg · hr/L [22].

This study did not take into account the concurrent antibiotics (C-penicillin and ampicillin) since these antibiotics demonstrate a time dependent properties and doses need to be administered more frequently to achieve the desired pharmacodynamic effect [32-33]. As such, these two drugs are dose rather conventionally in order to optimize duration of exposure [32]. Gentamicin efficacy is concentraton dependent and doses for neonates needs to be individualize according to kidney function and disease condition [3,[27,29,30]]. The differences in dosing regimen can affect the AUC/MIC ratio and its efficacy [33]. The rational of the combination of gentamicin and ampicillin is beneficial for the synergistic effect [3,31] due to these antibiotics have different microorganism coverage [31].

The retrospective study design gathered data for the year of 2011. Records of MIC of the studied organisms were not documented and were not retrievable. Hence, the MIC values quoted from the literature for specific microorganism (CoNS and *Klebsiella pneumonia*[13-14]*)* were used.

CONCLUSIONS

Both groups show 100% treatment successful rate with median treatment duration of 3 days. AUC/MIC ratio is not a determinant to associate Garasent® effectiveness in prevention EOS. However, higher AUC/MIC ratio can potentially increase the risk of toxicity.

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APPENDIX 1

Elimination rate constant, Ke (hr^{-1}) = ln (Cpost/Cpre) / τ - (t post-t pre) (τ = Time interval) Half life, $T_{1/2}$ (hr) = 0.693 / Ke

Concentration maximum, Cmax (mcg/ml) = Cpost $e^{Ke(t')}$ (t' = t post – t pre)

Concentration minimum, Cmin (mcg/ml) = Cmax $e^{-Ke(\tau)}$

Volume of distribution, Vd (L) = Dose / (Cmax-Cmin)

Clearance, CL (L/hr) = Ke x Vd

Area under the curve, AUC (mg·hr/L) = Dose / CL

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