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PHARMACOKINETIC SIMULATION AND OPTIMIZING GENTAMICIN DOSING IN PEDIATRICS

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Aim: *This study was conducted to optimize gentamicin (genta) use in paediatrics incorporating the estimation of serum drug concentrations and customized pharmacokinetic (PK) simulations.* ***Method:*** *66 patients (age 1-144 month) were enrolled in the study. They received gentamicin 2-2.5 mg/kg every 8 hr. (TID regimen). Serum genta concentrations within one dosing interval of dose 3 and dose 4 were determined using an immunoassay; blood samples were collected at 30 minutes after the end of infusion while a trough level sample was collected just before the next dose. Customized PK simulation analysis was based on the following assumptions: Single-compartment model, first-order elimination, and repeated short time IV infusion. PK parameters and simulation of genta peak/trough levels after various regimens were estimated and compared statistically.* ***Results:*** *About 65% of the patients showed subtherapeutic peak genta levels (less than 6 ug/ml) during the dosing intervals. Potentially toxic trough levels (>1 ug/ml) were observed in two patients. Neonates (1-12 months) showed a relatively higher mean genta volume of distribution (Vd), 0.51±0.18 L/Kg, vs 0.37±0.13 ($p<0.05$) in children (>1-12 y). Half-life in both groups was comparable (about 3 h). Simulation suggests BID regimens will provide the best theoretically overall peak/trough targets.* ***Discussion:*** *In children, a higher volume of distribution of genta could be associated with the lower serum peak levels due to the conventional dosing regimen (TID).* ***Conclusion:*** *Optimal dosing regimen in pediatric patients can be designed to achieve target high peak, low trough levels based on simplified customized PK simulations.*

INTRODUCTION

Aminoglycosides (AG) are bactericidal antibiotics, of which genta is frequently used for the management of many serious gram-negative infections in adults, children, and neonates. However, it needs to be emphasized that their use is associated with the dilemma of nephrotoxicity and ototoxicity[1]. Distinctly, this is surmounted to a great extent by, therapeutic drug monitoring (TDM) to ensure efficacy and minimize toxicities[2-5]. Interestingly; AG significantly revealed concentration-dependent efficacy, the post-antibiotic effect that supports adopting once daily (OD) dosing in adults[6]. Nevertheless, a considerable dispute has been expressed regarding the effectiveness of once-daily dosing of AG in children. A cohort study has revealed a higher incidence of ototoxicity following the OD regimen of AG in children associated with risk factors[7]. The analogous finding was convincingly reported in other studies utilizing AG in critically ill paediatrics[8] and those suffering from cystic fibrosis[9]. The present work aimed to provide a simple approach to optimize the dosing of genta in children with normal renal function.

METHODS

The present prospective study was implemented at the pediatric department, King Abdulaziz University Hospital (KAUH), Jeddah, KSA. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, KAUH.

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Inclusion Criteria

Neonates aged 1-12 m, children 13-144 m who received genta as an empirical treatment for gram-negative infections, were included in the study. Monitoring of genta level was a part of routine clinical care at KAUH. The guidelines for genta dosing allow a range of doses given the diversity of pathogens, severity of infections and patients characteristics[10]. The dosing regimen is the sole responsibility of the clinician in charge.

According to the FDA guidance (1998), the pediatric population are classified as: neonates (birth to 1 month), infants (1 month to 2 years), developing children (2-12 years), and adolescents (12-16 years)[11]. The present study focusses on, developing children, we will use the term (Children) throughout this article.

The exclusion criteria

Those patients who had missing peak or trough levels; and those who received drugs that impair renal function or have congenital anomalies. Furthermore, relevant demographic, renal function test, co-medications, dosing regimen, and sampling time of genta, were retrieved from patients' files.

In the present study, the TID regimen (2-2.5 mg/kg; every 8 hr.) was implemented.

Samples for the peak (Cmax) genta level were taken after the 3rd dose; 30 minutes after the end of infusion (post-distribution phase) and the samples for trough level (C_{min}) were taken 10-15 min before the fourth dose.

Also, the genta level was analyzed by a fully-automated immunoassay procedure using a homogenous particle enhanced turbidimetric inhibitory immunoassay technique (PETUNIA) with Dimension Clinical Chemistry System (Stream lab – Dad Behring). Calibration and analysis were performed as specified by the reagent manufacturer. All specimens were tested within a few hours. Accuracy of analysis was assured by the daily running of three levels of quality control samples (QC). The coefficient of variation was less than 5%.

PK analysis

An Excel-based program was developed (Excel 2016 and visual basic) to estimate the volume of distribution (Vd), elimination rate constant (k), and half-life. The estimated PK parameters were used for simulation of concentration vs time profile of assumed dosing regimen and minimum inhibitory concentration (MIC) of 1 ug/ml. (supplementary material). The simulation aims to visually demonstrate achievement of the therapeutic peak; defined as 8-10 times MIC, therapeutic trough <1 ug/ml. The low or undetectable level should not exceed 8 hrs (the acceptable time of the post-antibiotic effect of gentamicin)[12].

The principles of estimation assumed that; genta distribution follows a one-compartment model and it was eliminated by the 1st order kinetic process (equations 1-5)[7&13].

Estimation of elimination rate constant (K)

$$K\ (hr^{-1}) = \frac{\ln\ln\left(\frac{C_1}{C_2}\right)}{t_2 - t_1} \qquad (1)$$

C_1= peak level (0.5 hr. after the end of infusion), C_2= pre-dose or trough level, (t_2 - t_1) = Time difference between the two samples.

For practical purposes Css was assumed to be attained after 3 doses, i.e., in our study, the samples were taken after the 3rd dose & before the 4th dose).

Estimate half-life ($t_{1/2}$) & Elimination rate constant (K)

$$K = \frac{0.694}{t_{1/2}} \qquad (2)$$

Estimation of Vd (L/kg)

$$Vd\left(\frac{L}{Kg}\right) = \frac{D\left(1 - e^{-Kt_i}\right)}{K \times t_i\left[C_1 - \left(C_2 \times e^{-Kt_2}\right)\right]} \qquad (3)$$

D= Dose of genta (mg/kg); ti = infusion time (0.5 hr.), e= base for Ln.; t_2= time of the 2nd sample (trough).

Prediction of genta level at any time post-dose

$$\left(C_1\right) = \frac{D \times \left(1 - e^{Kt_i}\right)}{K \times Vd \times t_i} \times \frac{1}{1 - \left(e^{-K\mathrm{T}}\right)} \qquad (4)$$

T (tau)= dosing interval (hr.)

$$C_x = C_1 \times e^{-Kt_x} \qquad (5)$$

t_x: sampling time for C_2, (x hr. post-dose).

Statistical analysis

Statistical analysis was performed using a statistical package program (SPSS, version 22). Pharmacokinetic parameters are presented as the means ± standard deviation (M±SD) independent sample t-test two-tailed, was used to compare mean PK values, $p< 0.05$ was considered as significant.

RESULTS AND DISCUSSION

Results

In this study, sixty-six pediatric patients were enrolled prospectively. Demographic and relevant clinical data are summarized in tables 1&2. Notably, chest infection represented a major reason for treatment with genta followed by the post-surgical procedure.

Table 1: Demographics; genta dose and baseline serum creatinine of pediatric patients (n= 66).

		Children	Infants
Age (month)	Mean	53	1.9
	SD	39.7	1.7
	Range	13-144	1-6
Weight (Kg)	Mean	15.7	4.1
	SD	13	0.58
	Range	6.2-60	2-3.2
Dose mg/kg/8 hr.	Mean	2.2	2.47
	SD	0.46	1.1
	Range	1-2.9	2-3.2
Basle serum creatinine Mmol/L	Mean	34.7	33.5
	SD	5.7	10.4
	Range	28-45	24-43

Table 2: Indication of genta and concomitant antibiotics in pediatric patients (n= 66).

		No of patients	%
Disease	Chest infection	52	78.8
	Post-surgical procedure	6	9.1
	Sepsis	2	3.0
	Urinary tract infection	4	6.1
	Endocarditis	1	1.5
	Otitis media	1	1.5
Concomitant antibiotics	Penicillin	42	63.6
	Cephalosporin	24	36.4

Furthermore, all patients received IV penicillin or cephalosporin in addition to genta. Renal function was monitored by measuring serum creatinine, (S. Cr) & blood urea nitrogen (BUN). Although reporting adverse effects were beyond the scope of this study, no mortality, or serious adverse effects to genta were documented. Few patients showed mild elevation of S. Cr (within 10% of baseline level) although they have a therapeutic genta level.

Subsequently, the patients are further subdivided into two groups according to their ages, for pharmacokinetic analysis. Group 1: infants (1-12 months) & group 2: children (13-144 months).

Data of determining (actual) peak and trough genta levels and the estimated PK parameters are presented in tables 3&4, respectively. Only 35% of the patients showed a peak genta level within the reference range (6-12 ug/ml). The incidence of low peak genta level was higher in infants compared to children. The mean trough genta level in both groups is potentially toxic (>1 ug/ ml.).

Table 3: Genta plasma level in pediatric patients, TID regimen (n= 66).

		Level ug/ml	No	%
Peak	Within range	6-12	23	34.8
	Subtherapeutic	<6	43	65.2
Trough	Within range	<1	64	97.0
	Potentially toxic	>1	2	3.0

* Ref range for multiple daily dosing: peak 6-12 ug/ml L, Trough <1 ug/ml

Table 4: Estimated PK parameters of genta in pediatric patients (Mean± SD).

	Dose mg/kg	Peak level (ug/ml)		Trough ug/ml	Vd L/Kg	$t_{1/2}$ (hr.)
		Therapeutic	Sub-therapeutic			
Infants: (1-12 m, *n*= 24)	2.47±1.1	10.8±2.99	56%	1.7±0.84	0.51*±0.18	2.8±0.6
Children:(13-144, m., *n*= 42,)	2.2±0.46	12.02±2.53	38%	1.29±.93	0.37±0.13	2.6±0.8

a: Reference range (ug/ ml) for gentamicin, TID regimen the peak 6-12, trough <1
*Significantly higher, t-test, $p< 0.05$.

It was observed that Vd (L/Kg) is relatively higher in infants (0.51 ± 0.18) compared to children (0.37±0.13) ($p< 0.05$). Figure 1 shows the simulation of genta level assuming BID, TID, OD regimen in children. It is noteworthy that the BID regimen is likely to provide higher peak & lower trough levels compared to the TID regimen. In contrast, once-daily dosing provided a higher peak level (about 20 ug/ml), but prolonged very low trough level (<1 ug/ml; more than 8 hr.) i.e., exceeds the time for the post-antibiotic effect of gentamicin[14].

Discussion

TDM and clinical PK are valuable tools to optimize the use of genta in clinical settings[15]. Taking into account (PK) and pharmacodynamic (PD) properties of genta, the achievement of high peak (8-10 times MIC) and very low trough (6-8 hr.) is an empirical guide for its optimal dosing[16].

The approach of using high dose and long dosing interval of AG was based on two fundamental PD characteristics of this class of antibiotics: The 1st is the post-antibiotic effect (PAE) which practically means continued bactericidal effect regardless of undetectable serum drug level for the specified time (about 3-8 hrs.).

PAE is restricted to certain strains of bacteria (gram-negative bacilli) and requires a normal immune system of the patient. In this context, for example, the duration of the PAE is reduced in the absence of polymorphonuclear leukocytes (PMNs). The 2nd PD characteristic of AG is the concentration-dependent efficacy, i.e. achievement of high serum peak concentrations (8-10 higher relative to the organism's MIC) likely to be associated with higher antibacterial efficacy (more rapid, and a higher percentage of bactericidal effect)[14].

Interestingly, a PK/PD modelling study based on retrospective data of genta suggested that once-daily dosing of 5-6 mg/kg/dose is adequate only to treat infections with gram-negative organisms having minimal inhibitory concentration less than 1 µg/mL but highlights the need to assess the safety of higher doses of genta in paediatrics[17]. Dose guidelines for OD aminoglycoside for pediatric patients without cystic fibrosis have been suggested given age as follows: 3 months to less than 2 years, 9.5

mg/kg; 2 years to less than 8 years, 8.5 mg/kg; and 8-18 years, 7 mg/kg[18].

However, the OD regimen in paediatrics was not adopted as a universal concept and some queries need to be answered. The available evidence demonstrates that efficacy, and probable nephrotoxicity are at least equivalent between OD and multiple daily-dosing regimens. More importantly, however, it identifies gaps in our knowledge about (1) the incidence of ototoxicity, (2) the appropriate dose (which varied from 4 to 7.5 mg/kg per 24 hours in the included trials)[7].

Furthermore, A wide inter-patient variation in genta elimination and Vd has been recognized. Several patient-specific variables are related to elimination and therapy influence serum level. These include renal function, age, fever, lean body weight, and route of administration[19-23]. Pediatric patients showed higher Vd which implies that a high aminoglycoside dose is required to attain adequate peak levels[24&25]. A comprehensive review of studies relevant to PK of genta in paediatrics indicated that the mean estimated genta Vd for newborns, infants, and children are 0.475, 0.35, and 0.33 L/kg, respectively. Although body composition and kidney maturation are identified as the main variables affecting the PK of genta in paediatrics. The authors emphasize to study the impact of other covariates, such as lean body weight,

concomitant medication, fever, and critical illness on aminoglycoside PK[24].

In the present study, the TID regimen (namely 2-2.5 mg/kg/8 hrs. slow IV infusion 30 min, rate = dose mg/kg/infusion time), automated infusion pump was utilized for pediatric patients enrolled in the study. Pediatric patients are known to have a higher ratio of body water relative to adults. About 70% of the bodyweight of term infants is water compared to 65% or 60% in children, and adolescents respectively[26]. Genta is a very polar drug, and its distribution is confined to extracellular fluids[27]. Given this low peak, genta levels are expected in a traditional dosing regimen 2.5 mg/kg/8 hrs. In the present study, there was an obvious relationship between high Vd and the high incidence of the low peak genta level. Patients with low peak levels of genta are common in clinical practice[28&29]. Genta is mainly eliminated by renal clearance so that it has a shorter half-life in children with normal renal function[27]. In the present study, the mean half-life of genta is about 3 hr. and not affected by the age of patients.

Many programs that use PK and simulations are of paramount importance to adjust the therapeutic regimen for drugs with a narrow therapeutic range. For example, AG, optimal software guide optimal dosing on an

individual basis based on an integration between the patient's profile (renal function, age, etc.); PD (e.g., post-antibiotic effect), and PK [e.g. Vd, k]. Moreover, it allows r estimation of individual PK parameters based on the measured drug levels. These data support design of optimal dosing regimen on an individual basis, i.e to achieve a target peak and trough AG levels[30].

In the present study, we used a simple Excel-based program to simulate various regimens given a pilot sample of pediatric patients who received genta but do not suffer other chronic diseases or renal impairment (supplementarily material).

Given the present results of high Vd and short half-life, PK simulation suggests 3.5-4 mg/kg BID. instead of 2-2.5 mg TID. (Fig 1). OD regimen provided a higher genta peak but prolonged a very low trough level.

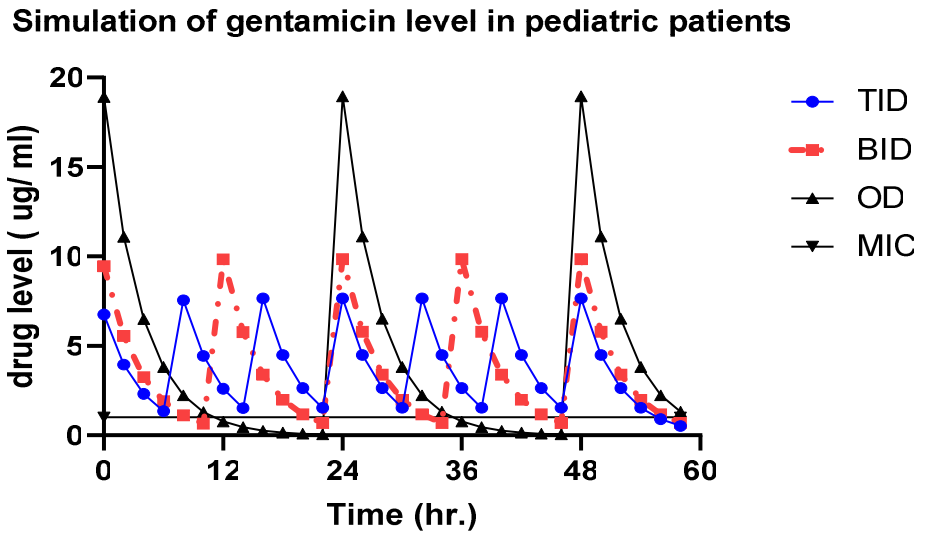

Fig. 1: Simulation of genta level at steady state after repeated IV infusion in Children (>1-12 y) in view of mean volume of distribution: 0.37 L/kg, half-life: 2.6 hr.), 2.5 mg/ kg, TID, 3.5 mg/kg BID and OD 7 mg/kg. The minimal inhibitory concentration of genta-sensitive bacteria (MIC) was supposed to be 1 ug/ml, optimal efficacy peak 10 times MIC. Recall the time of trough level < MIC, should not excessed 8-10 hr. (post-antibiotic effect). [see discussion for details].

The incidence of acute kidney injury (AKI) induced by AG in children was reported as 20-33%[31]. In the present study, nephrotoxicity due to genta was not documented and no clear association between genta serum levels and S. Cr levels was observed. Ali *et al.*, documented that S. Cr is a poor biomarker to follow the renal function in preterm neonates administer genta[32]. Marked elevation of S. Cr above its normal values is not significantly noticed until about 25-50% of kidney function has deteriorated. Therefore, using this biomarker alone to monitor kidney function means that the detection of nephrotoxicity may be late and may underestimate drug-induced nephro-toxicity[33&34]. Therefore, a more accurate renal function biomarker was suggested as a better early marker of drug-induced renal injury e.g., serum cystatin C; and β2-microglobulin[35]. Kidney injury molecule-1 was suggested as an early biomarker to identify AG-induced proximal tubular injury with promising results in clinical studies[36]. Cochlear toxicity of AG is less common in neonates and children compared to adults, the reported incidence was about 2% in neonates[37].

Conclusion

Given the PK parameters in the present study, the TID of 2-2.5 mg/kg is not likely to provide an adequate peak level in most pediatric patients with normal renal function. BID (e.g., 3.5-4 mg/kg) is more convenient and supposed to produce therapeutic gent levels. The Excel sheet was provided in the supplementary material to allow predication of other dosing regimens.

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Supplementary materials

PK-Simulation (software) for education & research purpose only.

https://drive.google.com/file/d/1-Vv2JDvQB3K-v5mwa_3ozvtTW0YlpGbP/view?usp=sharing

Disclaimer

The medical information and trends in this research are not intended to change any protocols and have not been evaluated clinically.

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محاكاة الحركة الدوائية للجنتاميسن في الأطفال واقتراح نظام الجرعات الامثل

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[2]قسم علم الأدوية ، كلية الطب ، جامعة الملك عبد العزيز ، المملكة العربية السعودية

الاهداف: أجريت هذه الدراسة الاستطلاعيه لتحسين استخدام الجنتاميسين في الأطفال بالاعتماد على قياس تركيز الدواء فى الدم واستنباط معاملات حركية الدواء ذات الصله وعمل محاكاة للتركيز للجرعات المقترحه باستخدام برنامج بسيط (الاكسل).

الطرق: تم متابعة ستة وعشرين طفلا مريضا (١ شهر الى ١٢ عاما) اعطى لهم الجنتاميسن بالحقن الوريدى البطىء لعلاجهم من اصابات بكتيريه. تم قياس تركيز الجنتاميسين في الدم باستخدام التلحليل المناعيى لقياس اعلى تركيز (٣٠ دقيقة بعد نهاية الحقن) وكذلك اقل تركيز (قبل الجرعة التالية مباشرة) وذلك بعد الجرعة الثالثه وقبل الرابعة. استند تحليل الحركية الدوائية للجنتاميسن إلى الفرضيات التالية: التوزيع يتبع نموذج الحجيرة الواحدة ، والتخلص من الدواء يتبع معادلات حركية الدواء من الدرجة الاولى ، ومعادلات حركية الدواء بعد الحقن الوريدي البطىء المتكرر. تم تصميم وتجربة برنامج إكسل لتقدير معاملات الحركة الدوائية حسب الفرضيات السابقة ومحاكاة مستويات الجنتاميسن الاعلى والادنى لمختلف الأنظمة االمقترحه (الجرعة اليومية مرة واحدة ، او تقسيمها الى جرعتان او ثلاث).

النتائج والشرح: لم يحقق ٦٥٪ من المرضى مستويات الجنتاميسن العلاجية (التركيز الاعلى > ٦-١٢ ميكروغرام/مل). أظهر الاطفال (١-١٢ شهرًا) متوسط حجم توزيع الجنتاميسين عال نسبيًا (٠,٥١ لتر/كجم) مقابل ٠,٣٧ في الأطفال (<١ -١٢ سنة). كان نصف العمر في كلا المجموعتين متقاربا (حوالي ٣ ساعات). أظهرت المحاكاة لنظم تعاطى الجرعات مرتين يوميا (٣ ونصف مجم لكل كيلوجرام) أفضل نتائج نظريه محتمله للتركيزات العلاجيه.يفسر الحجم الكبير لتوزيع الجنتاميسين في الأطفال غلبة مستويات الذروة المنخفضة المرتبطة بنظام الجرعات التقليدي ثلاث مرات يوميا.

الخلاصة: قياس مستوى الجنتاميسين فى الدم ، واستنباط معاملات حركية الدواء ، والمحاكاة للتركيزات المتوقعه تمثل وسائل عمليه تعين الاطباء والصيادله على اختيار نظام العلاج الامثل للجنتاميسين في الاطفال.