Use of Tigecycline in Neonates with Extensively Drug Resistant Organisms Infections in Neonatal Units of Queen Sirikit National Institute of Child Health

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บทคัดย่อ: การใช้ยาไทกีซัยคลินในทารกแรกเกิดป่วยที่พบการติดเชื้อดื้อยาหลายกลุ่มในหน่วยทารกแรกเกิด สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

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** แพทย์ประจำบ้านสาขากุมารเวชศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี แขวงทุ่งพญาไท เขตราชเทวี กรุงเทพมหานคร 10400

ภูมิหลัง: ยาไทกีซัยคลินเป็นยาปฏิชีวนะกึ่งสังเคราะห์ที่ออกฤทธิ์กว้าง แต่ข้อบ่งชี้ยังจำกัดเฉพาะผู้ป่วยที่มีการติดเชื้อดื้อยาหลายกลุ่ม ทารกแรกเกิดก็เป็นกลุ่มเสี่ยงต่อภาวะนี้ แต่ข้อมูลการใช้ยาไทกีซัยคลีนยังมีจำกัด **วัตถุประสงค์:** เพื่อศึกษาอัตราการรอดชีวิตของทารกแรกเกิดที่ติดเชื้อดื้อยาซึ่งได้รับการรักษาด้วยยาไทกีซัยคลิน ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี **วิธีการ:** การศึกษาเชิงพรรณนาแบบย้อนหลังโดยเก็บข้อมูลจากเวชระเบียนผู้ป่วยที่ได้รับยาไทกีซัยคลินในหน่วยทารกแรกเกิด สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ตั้งแต่วันที่ 1 มกราคม พ.ศ.2557 ถึง 30 กันยายน พ.ศ.2561 **ผล:** ทารกป่วยจำนวน 4,362 ราย เข้าเกณฑ์การศึกษา 82 ราย ค่าเฉลี่ยอายุครรภ์ของทารก 30.13 ± 4.42 สัปดาห์ เชื้อดื้อยาหลายกลุ่มที่พบบ่อยที่สุด 3 อันดับ ได้แก่ *K. pneumoniae* (54%), *P. aeruginosa* (24.1%) และ *A. baumannii* (19.5%) โรคที่ใช้ยาไทกีซัยคลินมากที่สุด คือ โรคปอดอักเสบ 34 ราย (41.46%) และ การติดเชื้อในกระแสเลือด 27 ราย (32.93%) อัตราการรอดชีวิตโดยรวมเป็น 86.58% การให้ยา 2 ขนาด (2 และ 2.4 มิลลิกรัมต่อกิโลกรัมต่อวัน) มีอัตราตายไม่แตกต่างกัน (p=0.44) ผู้ป่วย septic shock 3 ราย เกิดภาวะไตวายเฉียบพลันก่อนได้รับยาไทกีซัยคลินและเสียชีวิตในเวลาต่อมา **สรุป:** ยาไทกีซัยคลินสามารถใช้กับทารกแรกเกิดที่ติดเชื้อดื้อยาหลายกลุ่มได้ ความปลอดภัยจากการใช้ยาไทกีซัยคลินในทารกแรกเกิดป่วยยังต้องทำการศึกษาต่อไป

คำสำคัญ: การติดเชื้อดื้อยาหลายกลุ่ม ยาไทกีซัยคลิน ทารกแรกเกิด

Abstract

Background: Tigecycline is a broad spectrum antibiotic with restricted indications in paediatrics patients. Its use in clinical practice is reserved for cases with challenging infections due to multi-drug resistant bacteria. Limited data is available to determine the treatment outcome in neonates. **Objective:** To study the survival rate of antibiotic resistant newborn patients who were treated with tigecycline at Queen Sirikit National Institute of Child Health (QSNICH). **Method:** A retrospective descriptive study was conducted by extracting data from medical records of patients admitted in neonatal units of QSNICH who were treated with tigecycline between 1st January, 2014 and 30th September, 2018. **Result:** There were 4,362 neonatal admission during this period with 82 patients included in the study. The average gestational age was 30.13 ± 4.42 weeks. Three most common XDR pathogens identified were *K. pneumoniae* (54%), *P. aeruginosa* (24.1%) and *A. baumannii* (19.5%). Tigecycline

was used most frequently for the treatment of pneumonia; 34 cases (41.46%) and septicemia 27 cases (32.93%). The survival rate was 86.58%. Comparison of mortality rate between two different doses (2 and 2.4 mg/ kg/ day) showed no statistical significant difference (p=0.44). Three cases of septic shock developed acute kidney injury, before starting tigecycline, died later. **Conclusion:** Tigecycline can be used in neonates infected with extensive drug resistance organism. Safety of tigecycline use in neonates should be considered.

Keywords: Multidrug-resistant, Tigecycline, Neonate.

Introduction

Antimicrobial resistant bacteria including multiple drug resistance is increasing around the world. In 2011, World Health Organization (WHO) developed six action plans to elaborate threat of antimicrobial resistance in health care facilities and community[1]. In 2017, WHO again identified antibiotic resistant Gram-negative bacteria such as *Klebsiella pneumoniae, Acinetobactor baumannii, Pseudomonas aeruginosa* as critical priorities for new treatment[2]. A study from a neonatal intensive care unit (NICU) in Thailand found 64% of the enrolled cases were colonized by carbapenem-resistant organisms which were isolated within 3-20 days of admission (median of 7 days)[3]. Many cases with new episode or worsening of hospital-acquired infection while receiving carbapenem or broad-spectrum antibiotic are at risk of extensive drug resistant bacterial infection. Tigecycline is a broad spectrum, semisynthetic glycylcycline antibiotic with restricted approval indications in pediatrics. Its adoption as an off-label use in clinical practice is reserved for cases with challenging infections due to multi-drug resistant bacteria. Limited data are available to determine the treatment outcome of these pediatric patients especially in neonate. A systematic review about tigecycline treatment for carbapenem-resistant *Enterobacteriaceae* infections in adult reported that tigecycline combination therapy and high dose regimens may be more effective than monotherapy[4]. In a phase 3 clinical trial, mild adverse effects were reported in most patients, similar to placebo[5]. With limited treatment options, tigecycline, despite its cost, has been used as salvage therapy in combination with other drugs for critically ill neonates.

Objective

To study the survival rate of neonates with antibiotic resistant bacterial infection who were treated with tigecycline in neonatal unit of Queen Sirikit National Institute of Child Health (QSNICH).

Materials and Methods

A retrospective descriptive study was conducted by extracting data from medical records of patients admitted in neonatal units of QSNICH during 1st January, 2014 and 30th September, 2018. There were a total of 4,382 sick neonates admitted to the neonatal unit during this period. Sample size of 291 cases was calculated using the average survival rate of carbapenem resistant organisms in our neonatal unit (74.7%), with alpha error 0.05 and power of 0.8. However, 119 cases received tigecycline but analysis done on 82 patients in the 45 month-study period.

The indications for tigecycline prescription were identified as (1) culture directed prescription (2) failure with a previous antibiotic treatment (3) clinical sepsis while already receiving multiple antibiotic treatments.

Cultures were performed before tigecycline treatment was started. After identifying the pathogenic microbial isolates, antimicrobial susceptibility was determined according to the institute's laboratory standards criteria. Eradication was defined as negative culture in the repeated culture of the same site. Clinical response was determined by the resolution of patient signs and symptoms, 'failure' if the patient died during tigecycline treatment.

Statistical analysis

Categorical variables were analyzed as frequency (percentage) and continuous variables as mean ± standard deviation. Pearson's chi-square test was used for comparison of the categorical variables of patient subgroups. Statistical significance was considered at two-sided 5% level. Data were analyzed using IBM SPSS version 16.0 for Windows (IBM Corp., Armonk, NY, USA)[6]. The study protocol was approved by the Ethics Committees of Queen Sirikit National Institute of Child Health

Results

Demographic characteristics

A total of 4,382 neonates were admitted in neonatal units between 1st January, 2014 and 30th September, 2018. According to the hospital database, a total of 119 cases received tigecycline during the study period. Those without positive bacterial culture, positive for *Staphylococcal* spp, and those who received less than 5 days of tigecycline were excluded (Figure1).

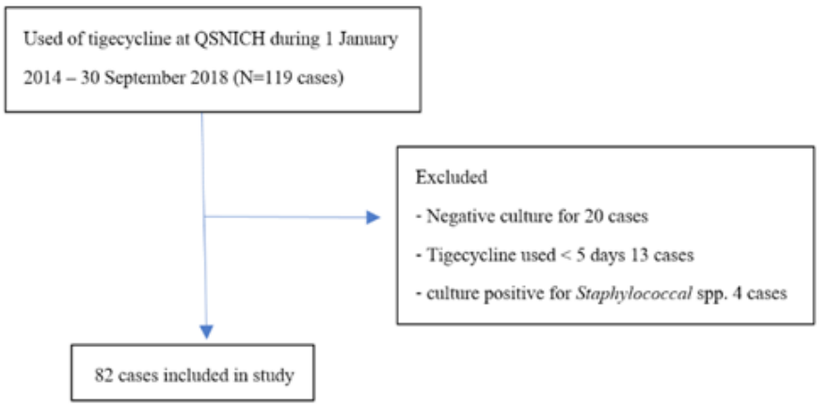

Figure1 Flow chart of patient's selection

Thus eighty-two (1.9%) patients were finally included. The overall survival rate was 86.5% (n=71). The average gestational age was 30.13 ± 4.42 weeks with mean birth weight of 1384.8 ± 854.66 gram. Forty-eight (58.54%) patients were male. Sixty-two (75.61%) patients had undergone assisted ventilation. Since 2014 perinatal swab culture has been routinely obtained from all new admissions to the neonatal unit as well as all neonates who have been in contact with carbapenem resistant *Enterobacteriaceae* (CRE) positive infants as infection surveillance. The median postnatal age of CRE colonization was 16.5 days (IQR, 10 - 26). The median days of microbial colonization prior to development of disease was 2 days (IQR, 0 - 8.5 days) (table 1).

Table 1 Demographic data of neonates treated with tigecycline

Demographic data	Total (N=82)
Gestational age, (wk)	30.13 ± 4.42
Birth weight, (g)	1384.8 ± 854.66
Male, n (%)	48 (58.54)
Assisted ventilation, n (%)	62 (75.61)
Postnatal age of CRE isolated (day)	16.5 (10-26)*
Day of colonization prior to development of disease (day)	2 (0-8.5)*

*median (IQR)

Pathogenic microbial strains

A total of 113 pathogenic microbial strains were isolated, all were carbapenem resistant strains. *Klebsiella pneumoniae* was the most frequent pathogen identified 61 (54%), followed by *Acinetobacter baumannii* [22] (19.5%), *Pseudomonas aeruginosa* 28 (24.1%) *Enterobacter* spp[1] (0.9%) and *Stenotrophomonas maltophilia* 1 (0.9%). Thirty-eight strains were isolated from the trachea, nineteen from urine, sixteen from blood, six from perianal, two from stool and one from the skin wound. There were 28 of 82 patients (34.15%) with multiple microbes isolated. Three common pathogens causing multiple infections were *K. pneumoniae, A. baumannii and P. aeruginosa;* all of them were prior treated with meropenem and colistin. The survival rate of patients with multiple microbial infections was excellent, 25 cases (89.29%) after inclusion of tigecycline in the treatment regimen as combination therapy (table 2).

Table 2 Survival rate of multiple infections cases with combination therapy, n (%)

Multiple microbial isolates	N=82	Survival rate
K. pneumoniae + A. baumannii+ P. aeruginosa	6 (7.3)	5 (83.3)
K. pneumoniae + A. baumannii	10 (12.2)	9 (90.0)
K. pneumoniae + P. aeruginosa	12 (14.6)	11 (91.7)
total	28 (34.1)	25 (89.3)

A high percentage of antibiotic resistant pathogens were identified. All *were* XDR pathogen (Table 3). Five of the ten *K. pneumoniae* cases were resistant to tigecycline but they were treated with tigecycline combined with meropenem and colistin, all of whom survived.

Table 3 Percentage of drug resistant *microbes*

Antibiotic-discs	*Klebsiella pneumoniae* n/ N (%)	*Acinetobacter baumannii* n/ N (%)	*Pseudomonas aeruginosa* n/ N (%)
Imipenem	57/ 58 (98.3)	18/ 18 (100.0)	20/ 20 (100.0)
Meropenem	58/ 58 (100.0)	18/ 18 (100.0)	21/ 21 (100.0)
Ertapenem	8/ 9 (88.9)	1/ 1 (100)	2/ 2 (100.0)
Ceftazidime	2/ 5(40.0)	11/ 12 (91.7)	2/ 5 (40.0)
Piperacillin/ tazobactam	11/ 12 (91.7)	4/ 4 (100.0)	2/ 3 (66.7)
Ciprofloxacin	29/ 3 2(90.6)	10/ 11 (90.9)	10/ 14 (71.4)
Amikacin	9/ 13 (69.2)	1/ 3 (33.3)	3/ 6 (50.0)
Tigecycline	5/ 10 (50.0)	1/ 6 (16.7)	1/ 5 (20.0)
Colistin	0/ 3 (0.0)	0/ 2 (0.0)	0/ 3 (0.0)

Tigecycline treatment regimen and Clinical response

There were 3 of 16 (18.7%) neonatal death in the maintenance dose of 2 mg/ kg/ day group compare to 8 of 66 (12.1%) neonatal death in the group of 2.4 mg/ kg/ day with no significant differences (p=0.44). The most frequent indications for tigecycline treatment in non-sepsis group were pneumonia 34 (41.46%), urinary tract infection 15 (18.29%) and sepsis 27 (32.93%) (table 4). Total survival rate was 86.58%. In the sepsis group, 22 (81.5%) survived compared to the non-sepsis group survival of 49 (89.1%) with no significant difference (p=0.34). Three cases of septic shock without prior colonization had sudden deterioration and acute kidney injury while being treated with tigecycline. All 3 died after 7 days of treatment.

Table 4 Survival rate by type of infection

Type of infection N=82	Total N (%)	Survive N (%)
Sepsis	27 (32.9)	22 (81.5)
Non-sepsis	55 (67.0)	49 (89.1)
- Pneumonia	34 (41.5)	31 (91.2)
- Urinary tract infection	15 (18.3)	12 (80.0)
- Colonization	4 (4.9)	4 (100.0)
- Enterocolitis	1 (1.2)	1 (100.0)
- Rupture meningomyelocele	1 (1.2)	1 (100.0)

Discussion

According to the World Bank report, global 2018 neonatal mortality rate was 17.7, while it was 5 per 1000 livebirth in Thailand[7]. Report from 12 health regions of Thailand in 2018, showed neonatal sepsis (3%) as the fifth most frequent cause of neonatal death[8]. In Thailand, five major antibiotics resistant bacteria were *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Methicillin-resistant Staphylococcus aureus*. These add to the health burden resulting in additional morbidity, mortality and economics loss[9]. The authors present a series of sick neonates who received tigecycline as a salvage therapy for serious infections due to XDR bacteria. The present study is the

largest sample size of neonates with a high survival rate of 86.6% despite the extremely young age group. Compared to existing studies among pediatric populations; the survival rate in Song[10] was 86%, 53.8% in Losifidis[11], and 75% in Zeng[12]. Rate of carbapenem resistance in *Klebsiella pneumoniae* in our study is very high. Survival rate of those receiving tigecycline is also high. Roberts[3] study in an NICU in Thailand found that CRE were isolated within 3-20 days of admission (median of 7 days), compared to the median day of our study was 16.5 days. Though there were significant differences in survival rate among those with or without loading dose of tigecycline. Outcome between two different maintenance doses of tigecycline showed no significant difference. The survival rate of multiple infection cases using combination therapy in our study was excellent as per the suggestion of Dalkos[13] and Ni[4]. Three cases (3.6%) developed acute renal failure during the treatment which was unclear whether it was related to underlying condition or medication. The limitation of this study was the nature of study as a retrospective case review not a clinical trial, and inadequate sample size. Due to the aggressive implementation of infectious control strategy, the XDR pathogens have decreased in past one year after the study and tigecycline use was also declined.

Conclusion

Tigecycline can be used safely in neonate with extensive drug-resistant infection. The survival rate is high with good response. The outcome was not different by using two recommended dose groups.

What is already known on this topic?

Antimicrobial resistant bacteria including multiple drug resistance is increasing around the world. Tigecycline is a broad-spectrum antibiotic with restricted approval indications in paediatric patients.

What this study adds?

Tigecycline can be used safely and effectively in neonates who got extensive drug resistance organism infection.

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Conflicts of interest

The authors declare no conflict of interest.

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